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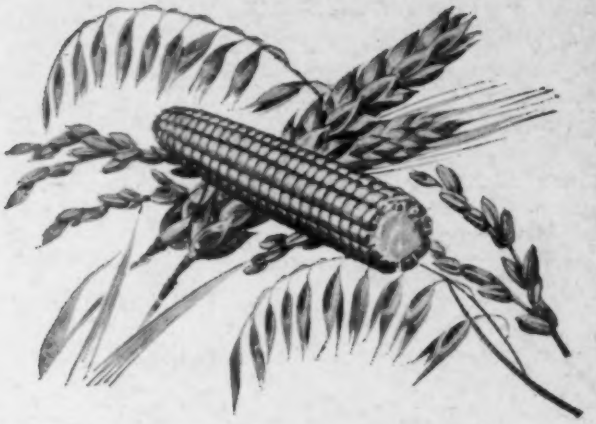

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The Journal of Pediatrics

VOL. 24 MARCH, 1944 NO. 3

Original Communications

HYPERIMMUNE WHOOPING COUGH SERUM

FURTHER STUDIES

AIMS C. MCGUINNESS, MAJOR, MEDICAL CORPS, ARMY OF THE UNITED STATES, JANET G. ARMSTRONG, AND HARRIET M. FELTON, M.D.
PHILADELPHIA, PA.

FROM results described in 1940,[1] hyperimmune human serum appeared to be a valuable adjunct in the prevention and treatment of whooping cough. The present report summarizes the data which have subsequently become available concerning the clinical use of this serum and its method of preparation and assay.

PASSIVE IMMUNIZATION OF EXPOSED SUSCEPTIBLE INDIVIDUALS

As may be seen in Table I, data are available on 308 patients receiving hyperimmune serum following exposure to whooping cough. None of the infants had received any form of active immunization against whooping cough and none of them had had the disease. The cases are divided according to the duration of exposure and the result obtained. A "very mild disease" indicates a mild cough of short duration without whooping or vomiting. In most instances these cases would have remained unrecognized had it not been known that an exposure had occurred. A "mild disease" indicates an attack of relatively short duration with whooping but no vomiting. In those cases listed under "Typical Disease" the infants had what appeared to be unmodified whooping cough. That the duration of exposure is a very important factor is clearly demonstrated by the results obtained. The fact that 67.9 per cent of 137 children continuously exposed to whooping cough in the same household failed to contract the disease is considered significant, as one would expect not more than 10 or 20 per cent of thoroughly exposed individuals to escape the disease. When the group as a whole is considered, 78.6 per cent of 308 individuals failed to contract the disease, which is of interest, as it coincides almost exactly with the figure of 78.3 per cent of the eighty-three cases reported in January, 1940.

From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia.

TABLE I

WHOOPING COUGH PROPHYLAXIS (308 CASES)

TYPE OF EXPOSURE	NO DISEASE	VERY MILD DISEASE	MILD DISEASE	TYPICAL DISEASE
Intimate exposure—continuous (137)	93 (67.9%)	21 (15.3%)	10 (7.3%)	13 (9.5%)
Intimate exposure—short duration (112)	93 (83.0%)	9 (8.0%)	4 (3.6%)	6 (5.4%)
Casual exposure—including hospital (59)	56 (94.9%)	1 (1.7%)	1 (1.7%)	1 (1.7%)
All cases—(308)	242 = 78.6%	31 = 10%	15 = 4.9%	20 = 6.5%

Concerning the matter of dosage, it is considered of the utmost importance to give two injections of 20 c.c. each from three to five days apart in all children under continuous exposure regardless of age, the interval between injections depending upon the time following exposure that the first injection is made. If the first injection can be given within the first twenty-four to forty-eight hours following the initial exposure, the second injection may be given five days later. If the first injection is given more than two days after the initial exposure, the second injection should be given three days after the first. Many failures have been due to inadequate doses of serum. Twenty cubic centimeters of serum, especially the vacuum-dried serum which may be concentrated, may be given with ease and is well tolerated by the smallest infants. Young infants may be protected with as little as 10 c.c. of serum following casual exposure, but it is felt unwise to economize when there is any possibility of the exposure having been anything more than casual.

In passive immunization serum may be given intramuscularly or intravenously; the latter route produces somewhat less discomfort and may be preferred, especially in older children. In the great majority of the infants whose cases are reported here the injection was made into the muscles of the buttocks.

WHOOPING COUGH TREATMENT

Data are available on 442 infants and children treated with hyperimmune serum after the onset of paroxysms; 176 of these patients were 6 months of age or under and 236 were in the first year of life. Fifty-five patients were known to have bronchopneumonia at the time treatment was first instituted.

It is felt that the minimum course of treatment should be three 20 c.c. injections of serum at forty-eight-hour intervals regardless of age, making a total minimum dosage of 60 c.c. In many instances a fourth dose of 20 c.c. of serum is necessary from five to seven days after the third dose, for a relapse may occur at this time apparently due to the waning of passive immunity in the presence of a still active disease. In some seriously ill individuals several intravenous doses of from 50

to 100 c.c. of serum may be necessary. This is most often required in the presence of bronchopneumonia. While the majority of infants whose cases are reported here were treated by the intramuscular route, it is felt that in seriously ill infants the intravenous administration of serum is preferable. It may also be the route of choice in older children, as intravenous injection produces less discomfort.

Data on a number of patients are available which are not included here inasmuch as the dosages of serum employed were below those considered therapeutically effective, even though in a few instances improvement appeared to follow total doses of 40 c.c. An exception is made in the instances of the six infants who died, none of whom received as much as 60 c.c. of serum, inasmuch as it was felt that these cases should be presented in detail.

The results obtained in this series of cases have been evaluated as (1) excellent, (2) good, (3) moderate, (4) questionable, and (5) deaths. The number of cases falling into each group may be seen in Table II. The consistency of these results becomes apparent when they are compared with the first 100 cases reported in 1940. At that time 63 per cent of the cases fell into the excellent and good groups as compared with 70.2 per cent of the 442 cases reported at this time; 20 per cent of the cases fell in the group showing moderate benefit as compared with 19.9 per cent of the present group; and 14 per cent failed to show any benefit as compared with 8.6 per cent for the entire series of cases. There have been but three deaths among treated patients since the first report was made, bringing the total number of deaths to six. The fact that none of these six infants received as much as the minimum amount of serum recommended for the treatment of infants with uncomplicated cases is emphasized.

TABLE II

WHOOPING COUGH TREATMENT—ENTIRE SERIES (442 CASES)

RESULT	NUMBER OF PATIENTS	
Excellent	170 (38.5%)	70.2%
Good	140 (31.7%)	
Moderate	88	19.9%
Poor	38	8.6%
Deaths*	6	1.3%

*None of these cases received as much as the minimum recommended therapeutic dose of serum (60 c.c.). These are the only cases included in this series who received less than 60 c.c. of serum.

The distribution of the cases treated with respect to age and result obtained may be seen in Table III. There are shown 176 cases in infants 6 months of age and under with but five deaths, making the extremely low death rate in this age group of 2.8 per cent.

When one examines the data with respect to age group and results obtained, it will be seen in Table III that the results are strikingly

TABLE III

WHOOPING COUGH TREATMENT—GROUPED ACCORDING TO AGE (442 CASES)

AGE	RESULT	NUMBER	
6 months and under (176)	Excellent	70 } 124	70.5%
	Good	54 }	
	Moderate	35	19.9%
	Poor	12	6.8%
	Deaths*	5	2.8%
6 months to 1 year (60)	Excellent	27 } 44	73.3%
	Good	17 }	
	Moderate	12	20.0%
	Poor	4	6.7%
	Deaths	0	0.0%
Over 1 year (206)	Excellent	73 } 142	68.9%
	Good	69 }	
	Moderate	41	19.9%
	Poor	22	10.7%
	Deaths*	1	0.5%

*None of these infants received as much as the minimum recommended therapeutic dose of serum (60 c.c.). No other cases of infants who received less than 60 c.c. are included in this report.

parallel in all three groups with the exception that all but one of the deaths occurred in the youngest age group, which is to be expected, and that the percentage of those showing little or no response was a little higher among the older children. The older children, of course, received much less serum based on body weight than the younger ones. The original disease among the younger children was invariably much more severe than that occurring in those in the older age groups.

There were fifty-five infants among the 442 cases here reported known to have had bronchopneumonia before serum therapy was instituted. In Table IV is shown the distribution of the cases of these

TABLE IV

BRONCHOPNEUMONIA PRESENT WITH WHOOPING COUGH (55 CASES)
UNCORRECTED CHART SHOWING ALL CASES WITH KNOWN BRONCHOPNEUMONIA PRIOR TO TREATMENT

AGE	EXCELLENT OR GOOD	MODERATE	POOR	DEATHS
Under 6 months (30)	17*	9†	0	4‡
6 months to 1 year (12)	9*	2	1	0
1 to 2 years (9)	5*	2	1*	1‡
Over 2 years (4)	2	2*	0	0

*Five infants under 6 months of age also received sulfathiazole or sulfadiazine.
Two infants from 6 months to 1 year also received sulfathiazole or sulfadiazine.
One infant from 1 to 2 years (good) also received sulfathiazole or sulfadiazine.
One infant from 1 to 2 years (poor) also received sulfathiazole or sulfadiazine.
One infant over 2 years (moderate) also received sulfathiazole or sulfadiazine.
†One of these infants also received only 40 c.c. of serum.
‡None of these infants received a minimum therapeutic course of serum (60 c.c.).

fifty-five infants, which include ten infants given sulfathiazole or sulfadiazine in addition to the serum, one with an apparently moderate response who received only 40 c.c. of serum, and five who died, none of whom were given adequate doses. The corrected picture excluding those infants receiving sulfonamide therapy and those receiving insufficient serum may be seen in Table V. This is of interest in that it presents thirty cases of pertussis bronchopneumonia in children in the first year of life, including twenty infants 6 months of age and under, without a single death.

TABLE V

BRONCHOPNEUMONIA WITH WHOOPING COUGH
THIRTY-NINE CASES RECEIVING A MINIMUM OF 60 C.C. OF SERUM AND NO SULFONAMIDE

		EXCELLENT AND GOOD	MODERATE	POOR	DEATHS
Under 1 year of age (30)	Under 6 months (20)	12	8	0	0
	6 months to 1 year (10)	7	2	1	0
Over 1 year of age (9)	1 to 2 years (6)	4	2	0	0
	Over 2 years (3)	2	1	0	0
Total	39	25	13	1	0

An example of a case from each group including a brief abstract of the history of each infant who died is as follows:

GROUP I (EXCELLENT)

K. L., white male, 3 months of age, was first seen Aug. 6, 1942. He had been in constant contact with an older sibling in whom whooping cough had been diagnosed two weeks previously. The patient gave a history of paroxysmal cough of four days' duration and vomiting of three days' duration. Cyanosis of the lips and of the fingernails accompanied each paroxysm. In the preceding twenty-four hours he had had from fifteen to twenty severe paroxysms of coughing and had vomited from six to seven times. The infant was given three 20 c.c. intramuscular doses of serum—one on August 6, one on August 7, and one on August 10. In the twenty-four-interval following the first dose, the baby had ten paroxysms and vomited twice. On August 9 he had six paroxysms without cyanosis and vomited once. There was no vomiting after August 11. From August 12 the occasional cough was not severe, the baby was eating well, and his general appearance was much improved. On August 18 his cough was entirely gone, but the untreated sibling was coughing hard.

GROUP II (GOOD)

T. H., white female, 7 months of age, was first seen Dec. 12, 1941, with a history of a cough of twelve days' duration which had been paroxysmal and accompanied by vomiting for a week. For forty-eight hours preceding the first dose of serum the baby was having attacks of coughing and vomiting every hour day and night, cyanosis accompanying each paroxysm.

Three 20 c.c. doses of serum were given intramuscularly; one on December 12, one on December 14, and one on December 18. Twenty-four hours after the second

dose the coughing attacks decreased to about one every four hours. Rapid and marked improvement followed the third injection; there was no longer any cyanosis, and coughing attacks were infrequent and without accompanying vomiting. By December 24, twenty-four days after serum treatment was initiated, the baby was having only an occasional mild hacking cough.

GROUP III (MODERATE)

R. T., Negro male, 6 months of age, was first seen on Jan. 10, 1940. There was a history of cough of two weeks' duration which for one week had been paroxysmal and associated with vomiting. Attacks were occurring about every one-half hour. A diagnosis of pertussis with bronchopneumonia was made. On January 10, 20 c.c. of pertussis immune serum were given intramuscularly, with no improvement. A second dose of serum was not given for one week, but on January 17, 19, and 21, respectively, the baby was given 20 c.c. doses intramuscularly. On January 20 there was a marked decrease in the number of attacks but no apparent change in the severity; cyanosis was gone. On January 25 the vomiting had stopped but the paroxysms were still moderately severe although few in number. The respirations were normal. On January 30 the baby contracted a fresh cold and severe and frequent coughing attacks recurred. Another 20 c.c. dose of serum was given intramuscularly. In twenty-four hours there was marked improvement, and the baby coughed only once the night of February 1. The general appearance was much improved, and on February 3 the baby seemed well on the way to recovery.

GROUP IV (POOR)

B. S., white male, 2 months of age, was first seen on June 30, 1942, with a history of cough of ten days' duration. The cough had been paroxysmal for the preceding seven days and had been accompanied by vomiting for three days. In the twenty-four hours preceding the serum injection the baby had had twenty-five paroxysms of coughing accompanied by cyanosis and three attacks of vomiting.

Twenty cubic centimeters of serum were given intramuscularly on each of the following days: July 1, July 2, July 3, and July 6. No improvement was noted after the first three injections. After the fourth injection there was questionable improvement, the attacks dropping to ten to twelve in twenty-four hours. On July 14, three weeks and three days after the onset and two weeks subsequent to the beginning of serum therapy, the infant was having from six to seven moderately severe coughing attacks daily, not accompanied by cyanosis or vomiting.

GROUP V (DEATHS)—SIX CASES

1. R. D., white male, 2 months of age, was first observed Jan. 11, 1936, with a history of cough for about two weeks. He was having severe paroxysms of coughing at hourly intervals. Marked cyanosis occurred with each attack and râles were heard at both bases. The child appeared critically ill. On January 12 the râles in both lungs had increased considerably. *Twenty cubic centimeters of serum were given intramuscularly on January 12 at 6* P.M. *and an additional 20 c.c. of serum were given intramuscularly at 10* A.M. *on January 13,* at which time the child appeared moribund. Death occurred at 2:10 P.M. on January 13. It is obvious that this child received too little serum too late in the disease.

2. S., Negro female, 6 weeks of age, weighing 5 pounds, was first seen by the reporting physician on March 21, 1941, at which time she was probably in the second or third week of the disease and was having thirty paroxysms daily. There was no known pneumonia present, but x-ray studies were not reported. *The infant received two 10 c.c. doses of serum intramuscularly, one on March 23, 1941, and the second on April 8, 1941.* Death occurred from a complicating diarrhea on April 13, 1941.

The above two doses of 10 c.c. of serum each, spaced sixteen days apart, could hardly have been expected to alter the course of pertussis in this infant.

3. E. T., white male, 2 months of age, was first observed by the reporting physician on May 14, 1938, in the third week of the disease. He was critically ill with cyanosis and frequent weak paroxysms of coughing but did not whoop. *On May 15 the child was given a single 10 c.c. dose of hyperimmune serum* intramuscularly. Death occurred the following day and autopsy showed a bronchopneumonia. Culture from the lungs showed a predominating growth of *Hemophilus pertussis.*

4. H. R., Negro female, 18 months of age, was first seen by the reporting physician on Feb. 6, 1941, in the third week of her disease. The child was desperately ill, convulsive, and breathing rapidly with periods of apnea. She was given *one 20 c.c. dose of serum intramuscularly on February 6.* Death occurred thirty-six hours after admission. Autopsy showed edema and congestion of the brain.

5. A. B., white female, 2 months of age, was first seen on March 4, 1939, with an advanced pertussis bronchopneumonia. The child was having repeated paroxysms of coughing with severe cyanosis, and at times it was necessary to institute artificial respiration following paroxysms. *Two 20 c.c. doses of serum were administered intramuscularly, one March 4 and the other one, March 6.* Death occurred following a paroxysm March 8.

6. F. M., white male, 6 weeks of age. The mother of this infant began coughing from two to five days following delivery and continued coughing for seven weeks. The baby's catarrhal symptoms appeared within three weeks, and the disease rapidly became severe, with dyspnea and cyanosis. Oxygen was given and also 110 c.c. of serum from the mother. The infant's condition continued to be critical and *on about the twentieth day of the disease a single dose of 20 c.c. of pertussis hyperimmune serum was given intramuscularly.* The baby died twenty-four hours later.

The following case demonstrates the value of large intravenous doses of serum in a critically ill infant:

C. G., white female, 10 months of age, was admitted to the Children's Hospital of Philadelphia March 1, 1941, with a history of cough of three weeks' duration. For three days prior to admission the cough had become progressively more severe. On examination the child appeared extremely ill with cyanosis and dyspnea, and many fine râles were heard throughout both lung fields. A tentative diagnosis of bronchopneumonia was made, and the patient was put in an oxygen tent and given sulfathiazole.

On March 2, 1941, the baby's condition became much worse. Dyspnea and cyanosis had increased and the abdomen was greatly distended. The white blood cell showed 16,200 cells, with 62 per cent neutrophiles, 35 per cent lymphocytes, 2 per cent monocytes, and 1 per cent basophiles.

On March 4 the baby developed generalized convulsions, periods of apnea, and appeared moribund. A radical change had taken place in the blood count which now showed 85,000 white cells, 33 per cent neutrophiles, 65 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles. A diagnosis of pertussis bronchopneumonia was made, and a continuous intravenous infusion of hyperimmune serum was started. A total of 180 c.c. of serum were given within a period of twelve hours.

By March 6 the child had begun to show some improvement and she was given 75 c.c. of whole citrated blood. The convulsions had ceased, and the respirations were less labored and accompanied by less cyanosis.

On March 7 80 c.c. of hyperimmune serum were given intravenously, and by the evening of this day the condition was markedly improved and the child was removed from the oxygen tent.

By March 10 the child was convalescent and was eating a full diet with only an occasional paroxysm and no vomiting. Recovery from this point was uneventful.

This child received sulfathiazole in addition to serum, but up to the time serum therapy was started she grew steadily worse in spite of chemotherapy.

IMMUNIZATION OF DONORS AND ASSAYS OF SERUM

In a report made in November, 1941,[2] the immunization of donors with a vaccine containing 10,000 million organisms per cubic centimeter was described. In addition, the technique of performing the assay by agglutination was described in detail. Since March, 1942, a vaccine prepared according to the directions of Dr. L. W. Sauer and containing 15,000 million organisms per cubic centimeter has been employed. Each donor receives an initial course of four weekly injections of vaccine: ½ c.c. in each arm, 1 c.c. in each arm, 1 c.c. in each arm, and 1 c.c. in each arm. This makes a total of 7 c.c. of vaccine, being 2 c.c. more than the recommended total dose for active immunization of infants. About one month after the initial course of vaccine, as described above, the donor's serum is titrated, and if the agglutination titer is 1:2560 or higher, a bleeding for serum is made. At the time of each monthly bleeding a sample of blood is taken for determination of the donor's agglutination titer and, in addition, he is given 2 c.c. of vaccine (1 c.c. in each arm) in order to maintain his titer. It has been found that this method produces somewhat higher titers than were obtained when the vaccine containing 10,000 million organisms was employed, the average pools of serum having titers of 1:2560 as compared with 1:1280 heretofore.

The importance of carrying out regular titrations on the donors cannot be stressed too strongly, as some donors will never reach an agglutination titer of more than 1:320, even after repeated courses of vaccine.

COMMENT

The results here presented confirm the earlier reports from this laboratory indicating the value of hyperimmune human serum in passive immunization against and treatment of whooping cough. Frank, Patton, and Hamilton, in a report made in June, 1942,[3] emphasized the value of sulfathiazole in the treatment of whooping cough bronchopneumonia and stated that "30 consecutive patients with whooping cough bronchopneumonia were treated with large doses of hyperimmune whooping cough serum with a mortality rate of 20 per cent," and concluded that "hyperimmune whooping cough serum was found to exert no specific effects in the treatment but could be recommended as good supportive therapy." A careful analysis of this study reveals that a single injection of serum was given on admission, either intravenously or intramuscularly, in doses of from 2½ c.c. to 3 c.c. per pound of body weight. According to this schedule, a 6-month-old infant weighing 15 pounds would receive a maximum therapeutic dose of 45 c.c. of serum, and a 2-month-old infant weighing 8 pounds would receive but 20 c.c., even though seriously ill

with bronchopneumonia. As stated before in this study, no patient is considered to have had a minimum therapeutic course of serum unless 60 c.c. has been administered, and in the case of a critically ill infant from 100 to 200 c.c. of serum may be required.

In a personal communication, Frank[4] stated that no titers were run on the serum employed by him and his co-workers, but that titers on five pools subsequently prepared in a similar manner showed a titer of 1:500 in one pool and a titer "over 1:1000 in the other four." It is possible that better results might have been obtained by Frank and his co-workers if serum of a known high titer had been employed. That a high agglutination titer is of probable importance has been stressed for some time by Bradford and Scherp,[5] who have found that while some sera with low agglutination titers give good mouse protection, all sera with high agglutination titers invariably give good mouse protection. Miller, Silverberg, Saito, and Humber[6] have recently described a study in which the agglutination titers of a large number of children were followed over a period of several years in order to determine the relationship between the height of the agglutination titer and susceptibility to whooping cough. Among the eleven individuals in this group who were attacked with pertussis, the pre-exposure titers were very low, varying from 0 to 1:160. In conclusion, the authors state that "these observations suggest that whereas immunity may exist in the absence of demonstrable agglutinins, susceptibility does not occur in the presence of agglutinins in high titer."

While all but a few of the infants whose cases are included in this study were treated with hyperimmune serum which had been dried in vacuo from the frozen state, it should be emphasized that quite as good results should be obtained with high titer serum or plasma in liquid form.

Electrophoretic analyses of hyperimmune serum by Dr. Edwin J. Cohn of the Harvard Medical School[7] demonstrate that the antibodies in this serum are part of the gamma globulin fraction. It is possible that this fraction obtained in purified form by ethanol fractionation according to the method described by Cohn may yield antibodies in twenty- to fortyfold concentration.

There still appears to be some difference of opinion as to the role of toxin in the symptomatology of whooping cough and of pertussis antitoxin in its prevention and treatment. Strean, Lapoint, and Dechene,[8] in 1941, reported a study in which rabbit antiendotoxin or antiendotoxin plus antibacterial rabbit serum was employed in passive immunization of contacts. They concluded that "whilst the antiendotoxin alone was able in most cases to inhibit pertussis or at least produce an aborted attack, the combination of both antiendotoxin and antibacterial serum seems preferable."

Bullowa and Alterman[9] found that rabbit antitoxin was "capable of preventing whooping cough when given early in the incubation period and prior to the onset of cough, even though exposure continues." On

the other hand, they found the antitoxin "of little value in reducing paroxysms when the disease is established with a propulsive cough." In view of the apparent value of rabbit antitoxin in passive immunization, it has appeared important to determine whether better results may be obtained from the serum of human donors who have received both vaccine and toxoid. This study is now in progress.

Purified agglutinogen as described by Flosdorf and Kimball[10] and by Felton and Flosdorf[11] has been found to be markedly antigenic, and this substance either alone or in combination with vaccine and/or toxoid is being employed in the immunization of experimental groups of donors.

SUMMARY

1. Hyperimmune whooping cough serum obtained from donors immunized with phase I pertussis vaccine has been employed in passive immunization of 308 infants and children subsequent to exposure to whooping cough and in the treatment of 442 patients with whooping cough following the onset of paroxysms.

2. The results obtained closely parallel those reported earlier in the studies which indicated that the serum was of considerable value in the prevention and treatment of the disease.

3. The possible use of toxoid and/or purified agglutinogen for the development of hyperimmune serum, either one alone or in combination with vaccine, is in the process of investigation.

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STUDIES ON THE MINIMAL EFFECTIVE DOSE OF A WATER-SOLUBLE VITAMIN K SUBSTITUTE IN THE PREVENTION OF HYPOPROTHROMBINEMIA IN THE NEWBORN INFANT

SARAH HOOKER HARDWICKE, M.D.
ROCHESTER, N. Y.

INTRODUCTION

SELLS, Walker, and Owen[1] published the results of their studies on the effectiveness of 2-methyl-4-amino-1-naphthol (Synkamin) as a vitamin K substitute for the newborn infant in 1941. They found that a daily dose of from 1 to 2 μg of this substance was sufficient to maintain an adequate prothrombin level in the newborn infant; that a single dose of from 10 to 20 μg given in the first few hours of life held the prothrombin level "reasonably stable" throughout the first six days of life; and that a curative single dose of 1 μg gave a maximal, although slow, response. With doses of from 5 to 1,000 μg they reported that a maximal response was obtained within eight to ten hours, and from the figure published in this paper, it is apparent that in at least one patient a 5 μg dose produced a rise in prothrombin from about 42 per cent of normal to about 65 per cent in a little over two hours. These workers also found that from 5 to 10 Gm. of dried milk powder, used as a curative source of vitamin K, produced a response equivalent to that obtained with 0.5 to 1.0 μg of synkamin and concluded that milk contained enough preformed vitamin K to meet the minimal requirement of the newborn infant. In this work the prothrombin determinations were done by a micromodification of the one-stage "bedside test" devised by Smith and his co-workers,[2] and the test substance synkamin was administered intramuscularly, diluted as required with normal saline.

In 1940, Foster and his co-workers[3] published the results of their investigations of the antihemorrhagic activity of tetra sodium 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester, in which they found this substance to be one and one-half times as active as 2-methyl-1,4-naphthoquinone (menadione) on a molecular basis. However, on a weight-for-weight basis, they found this substance, owing to its much greater molecular weight, only 48 per cent as active.

The present study was undertaken in an effort to see whether, using Foster's diphosphoric acid derivative,* the order of magnitude of the prophylactic dose of a vitamin K-active substance found by Sells and co-workers could be confirmed, in a general way, for the use of this sub-

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*Furnished for this study through the courtesy of the Hoffmann-LaRoche Co., Nutley, N. J., as "Synkayvite" in 1 c.c. ampouls, each of which contained 5 mg. of this derivative.

stance in the prophylactic therapy of the newborn infant. Secondary objectives were to determine whether any untoward symptoms might be encountered in the use of this substance for the newborn infant and whether the material, when given by mouth, would cause vomiting as does the parent substance, menadione, and some of its water-soluble derivatives. (4-amino-2-methyl-1-naphthol, given orally in doses of from 1.0 to 2.0 mg. as the hydrochloride, apparently did cause vomiting in infants in our nurseries.)

METHOD

Babies born in the Rochester Municipal Hospital were included in the study* without regard for the prenatal history or the circumstances of delivery, which were not investigated until the experimental work was completed. Because it was desired to eliminate any seasonal effect which might make the various groups differ, babies were placed in the groups in rotation on their arrival in the nursery. This rotation was modified somewhat to keep the groups as even as possible, so that when a baby had to be dropped from the study because of artificial feeding or some other factor, the next baby to arrive took its place.

For various reasons, the study was divided into three periods: (1) May 11, 1942, to June 17, 1942; (2) July 6, 1942, to August 7, 1942; (3) August 26, 1942, to September 10, 1942. In the first period thirty-eight babies were studied; in the second, thirty-three; and in the last, sixteen.

All of the prothrombin times were done by either myself or Dr. Gretchen Hutchins, who kindly made the determinations for me on a few occasions. At least two control determinations were made each time determinations were made on the babies' blood. If these did not check within one second, further determinations were done until two determinations checked within these limits.

On arrival in the nursery each baby was assigned to one of the six groups used in the study. Those in the first group, O, were to receive no vitamin K; those in Group A were to receive 0.5 mg. of synkayvite per day; those in Group B, 0.05 mg.; those in Group C, 0.005 mg.; those in Group D, 0.0005 mg.; and those in Group E, 0.00005 mg. per day. In order that each baby might get his initial dose as soon as possible after birth, these doses were given, when I was not available, by the nurse in charge of the nursery, according to a prearranged schedule. The synkayvite was prepared by serial dilution with a 2 c.c. syringe and cool, previously boiled water, and fresh solutions were prepared every other morning. The solutions were made from the contents of the ampoules designed for intravenous use. Accordingly, dilutions of 0.5 mg., .05 mg., .005 mg., and .0005 mg. per cubic centimeter were prepared. These solutions were kept in brown glass bottles with rubber-

*Through the courtesy of staff members of the Department of Obstetrics, School of Medicine and Dentistry, University of Rochester, whose cooperation is hereby gratefully acknowledged.

topped dropper stoppers, and both bottles and stoppers were washed and boiled for fifteen minutes each day fresh solutions were prepared. These solutions were kept in labeled cardboard boxes at room temperature in the nursery. The droppers were supposed to deliver 20 drops per cubic centimeter and by actual test delivered between 17.3 and 20.4 drops per cubic centimeter. Two drops, or approximately 0.1 c.c. of the appropriate solution, were dropped directly onto the baby's tongue for each dose.

The micromodification of the Smith-Ziffren "bedside test"[2] developed here in this hospital by Lawson[4] was used throughout with but one slight modification. Lawson stirred the mixture of blood and thromboplastin with a small glass rod, while in this investigation the mixing was done by means of a jet of air blown through the pipette used, which set up circular currents, and, we believe, produced a quicker intimate contact of the two solutions. The variation in control times obtained was slightly greater than that found by Lawson, but individual control times checked closely.

It was expected from previous experience and the results reported by others[4, 5] that babies in several of the groups would exhibit "prothrombin times" indicative of serious deficiency of prothrombin. When the normal control time was about 20 seconds, Lawson[4] believed that vitamin K should be administered whenever the "prothrombin time" was over 75 seconds, and Pray,[5] using essentially the same method, believed that the danger zone lay between 70 and 100 seconds, although he found, as we and others have, that far more profound deficiencies might exist without the occurrence of bleeding. Accordingly, it was decided at the outset that any baby found to have a prothrombin time of more than 70 seconds should receive a therapeutic dose of the synkayvite. The first three babies to show such prothrombin times were given 1 c.c., or 5 mg., of this substance either orally or subcutaneously. No untoward reactions were noted by either route. By the time that the fourth baby to show such a severe hypoprothrombinemia was discovered, as it was apparent that small daily doses of synkayvite were effective, it was decided to try a much smaller dose, curatively, by mouth. One-tenth of a cubic centimeter, or two drops of the full-strength solution (equivalent to 0.5 mg.), was given once to each of six babies (all who, subsequent to the first three babies, were found to have severe deficiencies). These babies, with one exception, were followed for from three to eight days after receiving the synkayvite thus, and none showed any tendency to relapse, and none vomited after the dose.

Since the babies were born at various hours of the day or night and since it would be impractical to attempt to do the prothrombin determinations on each baby at a given interval after birth, an attempt was made to do all determinations at approximately the same time each day on all babies, and the predetermined dose of synkayvite was given to

each after all the determinations for the day had been made. Under such a scheme there was a varying interval between the initial dose and the second dose, though subsequently all doses for the babies being studied at the time fell at the same intervals. It was decided to give the second dose at the time of the routine morning determinations to a particular baby if that baby had not had its initial dose within the preceding twelve hours. Therefore the interval between first and second doses varied from twelve to thirty-six hours. Single prothrombin determinations only were done on the babies' blood unless there was an obvious fault with the first determination. In that case it was repeated and the second value used. Although this procedure leaves room for error, this error would all be in the direction of lowering the prothrombin times toward the normal, thus reducing the difference between the groups studied, as it has been shown that nearly all the errors in technique such as squeezing the part from which the blood is taken, the use of dirty glassware, etched glassware, etc. decrease the "prothrombin time."

The mean control prothrombin time was 19.7 seconds; the range, from 14.0 to 24.5 seconds. The average interval between daily determinations was 24.4 hours; the range, from fourteen to forty-one hours.

RESULTS

The "prothrombin times" found for each of the six groups of babies studied are shown graphically in Figs. 1 through 6. The "mean prothrombin time" represented by the dotted line in each figure was determined by interpolation of values to fifteen hours, twenty hours, twenty-five hours, and so on, after birth and by taking the mean of these values. Values obtained after the babies had been given therapeutic doses for dangerous deficiencies are not included in these means.

As will be seen from the figures, the maximum difference in the groups occurred early, and beyond the 140-hour mark there is little significant difference. Although not all of the babies were followed long enough to make the inclusion of their prothrombin times pertinent to the discussion, all values determined on these babies are included in the figures except when a baby was given artificial cow's milk feedings for any cause and except for one baby excluded entirely because it was later found that its mother had been given vitamin K during labor. It has been shown that babies who are given cow's milk feedings have significantly higher prothrombin levels in their blood than those entirely breast fed,[6] and therefore this exclusion is felt to be justified.

In Group A, 11 babies were followed through 140 hours; in Group B, twelve babies; in Group C, eleven babies; in Group D, fourteen babies; in Group E, eleven babies were followed through 140 hours and one through 130 hours; in Group O, twelve babies were followed through 140 hours.

In Group A all prothrombin times were below 40 seconds; in Group B, all were below 40 with one exception: one baby's prothrombin time rose from a level of 33.6 at four hours to 67.2 at thirty-one hours and dropped to 22.2 seconds at forty-nine hours. The significance of this will be discussed later. In Group C all prothrombin times were below

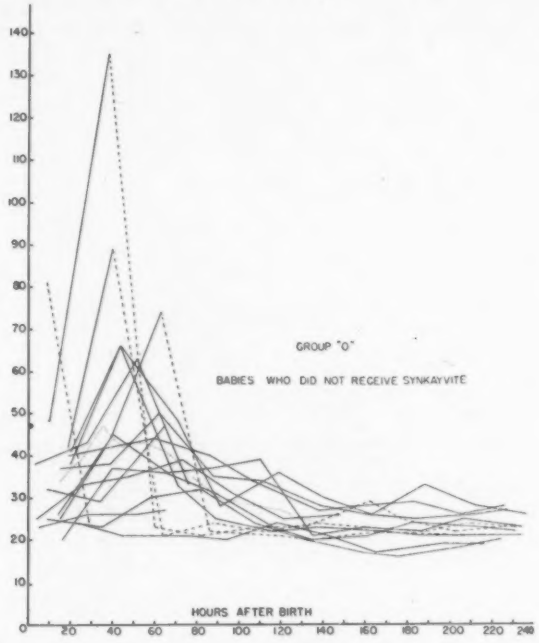

Fig. 1.—Ordinate shows prothrombin time in seconds. Abcissa shows number of hours after birth. Dotted line shows mean prothrombin time at five-hour intervals from 15 to 150 hours after birth. Broken line shows prothrombin times after the administration of therapeutic doses of synkayvite, given because of dangerously high prothrombin times.

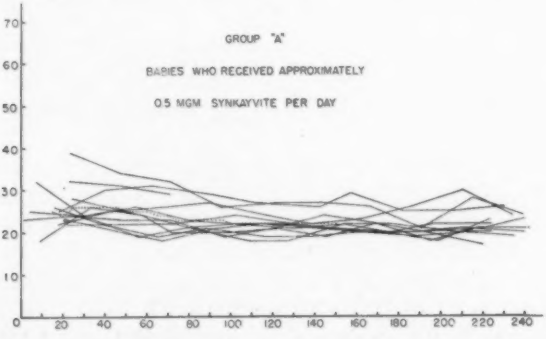

Fig. 2.—Ordinate shows prothrombin time in seconds. Abcissa shows number of hours after birth. Circles indicate single prothrombin times determined on each of two babies. Dotted line shows mean prothrombin time at five-hour intervals from 15 to 150 hours after birth.

40 seconds except for one baby, whose was 45 seconds ten hours after birth. In Group D, where the daily dose was only approximately 0.0005 mg., there is more variation apparent. There is one peak to almost 60 seconds at about sixty hours, and at eighty hours plus there are two values of over 40 seconds. In Group E, where the daily dose was only 0.00005 mg., there is no apparent difference in the prothrombin times from those found for the infants in Group O, to whom no vitamin K was given.

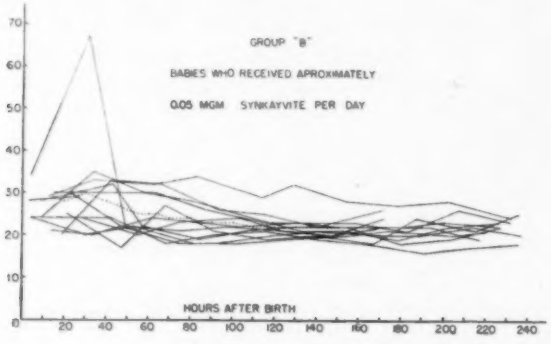

Fig. 3.—Dotted line shows average prothrombin time at five-hour intervals from 15 to 150 hours after birth.

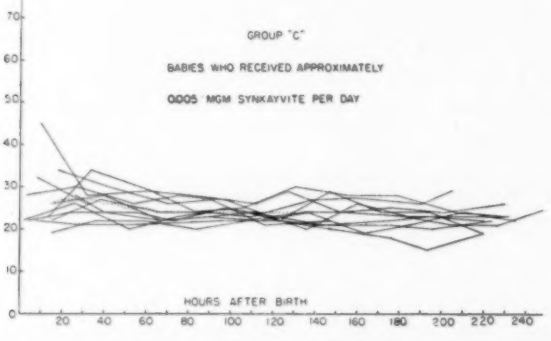

Fig. 4.—Dotted line shows mean prothrombin time at five-hour intervals from 15 to 150 hours after birth.

From Figs. 1-6 it is felt that one may conclude that a daily dose of 0.005 mg., or 5 μg of synkayvite (tetra sodium 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester), is sufficient to meet the requirements of the breast-fed newborn infant for vitamin K as a supplement, given orally, to that which he may obtain from breast milk or from supplies produced from bacteria in his own intestinal tract. We also believe that 0.0005 mg., or 0.5 μg, is probably sufficient to meet his *minimal* supplementary requirement, but further work would be necessary to exactly establish the lower limit of this requirement.

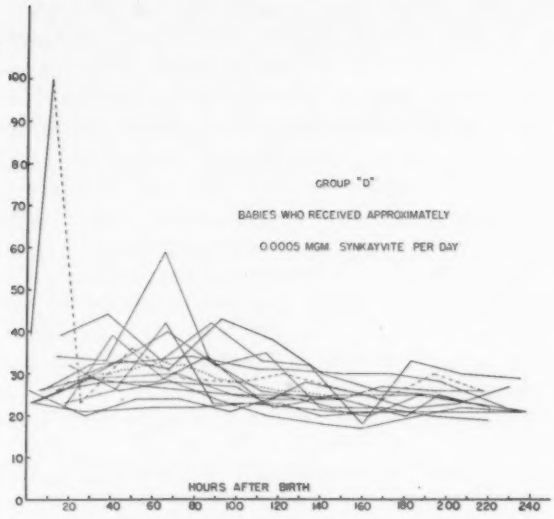

Fig. 5.—Dotted line shows mean prothrombin time at five-hour intervals from 15 to 150 hours after birth. Broken line shows prothrombin times after the administration of therapeutic doses of synkayvite, given because of dangerously high prothrombin times.

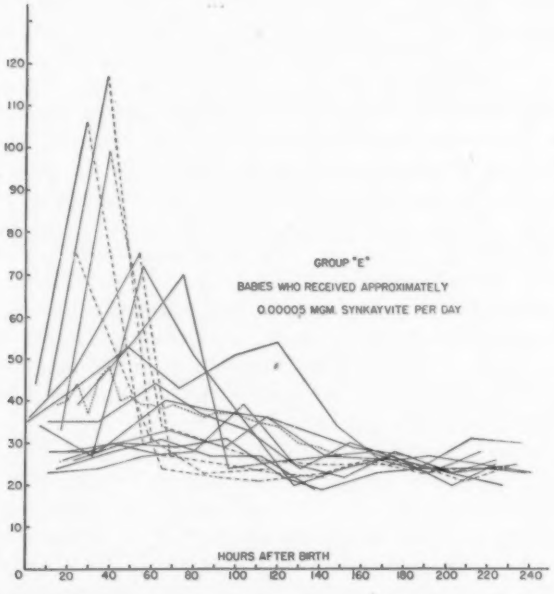

Fig. 6.—Dotted line indicates mean prothrombin time at five-hour intervals from 15 to 150 hours after birth. Broken lines indicate prothrombin times after therapeutic doses of synkayvite, given because of dangerously high prothrombin times.

There is evidence which suggests that the dose of 0.5 mg. of this substance is adequate as a single therapeutic or prophylactic dose in the prothrombin times of the six babies who were given such doses because of dangerously high prothrombin times. As can be seen from the charts, their prothrombin times fell promptly and remained low thereafter.

DISCUSSION

To decide whether or not the conclusions drawn above are valid, it is necessary to examine the data and conditions under which the babies were born to see whether there were present extraneous factors which might influence the results. It has already been mentioned that a number of workers concluded that the addition of cow's milk feedings to the infant's diet would lower the prothrombin time elevation commonly observed in the first few days of life. This factor has been taken care of by the elimination of figures obtained after artificial feedings had been added to a given baby's diet.

Barbiturates given to the mother as an analgesic during delivery or labor have been shown[7] to produce a greater prothrombin deficiency than is usual in the newborn infant. The barbiturates shown to have such an effect were sodium pentobarbital orally in 0.5 Gm. doses and sodium amyl bromoallyl barbiturate rectally in 1 Gm. doses. Examination of the records of the mothers of the babies studied here shows that a large number of them received either nembutal or seconal, and a few, sodium amytal, prior to delivery. The usual dose was 0.2 Gm. of nembutal and seconal and 0.4 Gm. of sodium amytal. In the paper referred to above, it was noted that administration of vitamin K was effective in preventing this effect of the barbiturates, and since essentially normal prothrombin values were found in Groups A, B, and C, we shall confine ourselves to the effect of the barbiturates in Groups D, E, and O. In these last three groups there were twenty-two babies whose mothers did not receive any barbiturate and twenty-three whose mothers received nembutal, seconal, or sodium amytal. The mean of the maximum prothrombin time observed for the babies whose mothers received no barbiturate was 54.5 seconds, while the mean of the maximum prothrombin times of those babies whose mothers did receive barbiturates was 49.0 seconds. Thus apparently the barbiturates did not prolong the babies' prothrombin times in this study.

In the calculation of these means, the values for two babies are omitted. In the group whose mothers had no barbiturates was the baby of a mother with placenta previa and prepartum hemorrhage. This baby had the highest prothrombin time of any of the babies in this study (135 seconds). In the other group was a baby who should have received no vitamin K at all and who, on the third day, received by mistake 0.05 mg. of synkayvite. This baby's maximum prothrombin time was 26.5 seconds. It was felt that inclusion of these values would distort the picture. Had they been included, obviously they would have made

the mean maximum prothrombin time of the babies of mothers who had no barbiturates even greater in proportion to those of babies whose mothers had received barbiturates.

Mineral oil administered orally has been shown to lower the blood prothrombin of experimental animals,[8] and also to affect adversely the blood prothrombin levels of human beings when given in doses of the magnitude usually used to combat constipation.[9] Javert and Macri, who discovered this effect of the oil in human beings, were unaware of the previous work on animals until after they had observed the relationship in their patients. They found, using the two-stage method of Smith, Warner, and Brinkhous, that three of nine patients who received from 15 to 30 c.c. of the oil twice or thrice weekly developed a deficiency, and seven out of ten patients who received from 15 to 30 c.c. two or three times daily also showed a deficiency. In the studies presented here no investigation of the prepartum history of the mothers in regard to their use of mineral oil was done. None of the mothers received mineral oil while in the hospital, but it must be admitted that some of them may have taken amounts at home which would conceivably affect the prothrombin values in their babies.

Although it was not expected that differences in the parity of the mothers would affect the blood prothrombin levels of their babies, the parity distribution was studied. As there seemed to be no significance in this distribution the details will not be included here. Table I shows the parity of those mothers whose babies showed great hypoprothrombinemia.

Finally, an investigation of the individual cases showing prolonged prothrombin times seems in order. As mentioned above, the highest prothrombin time recorded in this study was one of 135 seconds, recorded for baby girl B of Group O. This baby's mother had a marginal placenta previa, and the baby was delivered by version and extraction at the end of a twenty-nine-hour labor and after the insertion of a Voorhees bag. A 500 c.c. blood loss is recorded prior to the baby's birth, and it is thought that these facts might have influenced the baby's prothrombin level subsequently. Data on the other eighteen babies showing prothrombin times of over 50 seconds are tabulated in Table I. Aside from the placenta previa mentioned, there seem to be no factors shown which might have influenced the prothrombin other than possibly medical induction with castor oil and quinine. In one case the drug used for medical induction was not specified. As this was about the time when the use of quinine was stopped because of the war, it is not certain whether or not the patient received quinine.

It will be noticed that there was one baby in Group B whose prothrombin time is recorded as 67.2 seconds at thirty-one hours after birth. As there were no prothrombin times of this magnitude recorded for the infants in Group C, who received only one-tenth the dosage given the infants in Group B, it seems reasonable to assume that this

TABLE I

BABY	GROUP	MOTHER'S AGE (YR.)	PARITY	DELIVERY	BARBITURATE	MEDICAL INDUCTION	MAXIMUM PROTHROMBIN TIME
T.	O	23	P2G3	Vertex spontaneous	None	None	81
J.	O	26	POG1	Low forceps; 41½-hour labor	Nembutal	None	66.5
P.	O	39	P4G5	Vertex spontaneous	None	None	89.2
K.	O	27	P1G2	Low forceps for fetal distress after 12½ hours	None	Castor oil and quinine	66.1
L.	O	25	P1G2	Vertex spontaneous	None	"Medical induction two times"	74.0
M.	O	25	P1G2	Vertex spontaneous	None	Castor oil and sodium bicarbonate	50.5
B.	O	38	P5G8	Version and extraction for placenta previa; 500 c.c. blood loss prior to delivery	None	None	135
S.	O	31	P7G8	Vertex spontaneous	Seconal	Castor oil and nasal pituitrin tried six days previously	63.2
J.	B	27	P4G6	Vertex spontaneous	None	None	67.2
De L.	D	23	POG1	Low forceps because no progress in second stage	Sod. amytal	None	100
W.	D	21	P1G2	Vertex spontaneous	Nembutal	None	59.1
S.	E	23	P2G3	Vertex spontaneous	Seconal	None	53.9
H.	E	21	P1G2	Vertex spontaneous	None	None	99.2
C.	E	25	P1G2	Vertex spontaneous	None	None (Mother a congenital syphilitic, baby not)	117
R.	E	21	POG1	Vertex spontaneous	None	None	106.2
H.	E	33	P6G10	Vertex spontaneous	Seconal	None	74.9
S.	E	33	POG1	Low forceps because slow second stage	Seconal	None	70.0
R.	E	21	POG1	Low forceps because slow second stage	Seconal	None	75.0
P.	E	21	P1G2	Vertex spontaneous	None	None	71.8

high value is the result of an error, although it may not be. As the initial dose of vitamin K was not given by the same person each time, it is conceivable that the wrong bottle might have been used, or possibly that a dose was omitted. Unfortunately the facts cannot be determined.

SUMMARY AND CONCLUSIONS

A total of eighty-seven breast-fed newborn babies in the Rochester Municipal Hospital nursery were studied between May 11, 1942, and Sept. 10, 1942, in an attempt to establish an approximate minimal effective daily dose of synkayvite (tetra sodium 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester). They were divided into six groups, of which infants in five received doses of 0.5, 0.05, 0.005, 0.0005, 0.00005 mg. of the test substance daily, and infants in one of which served as controls. The substance was given orally.

The following conclusions are believed justified:

1. The minimal effective daily dose of this substance lies somewhere between 0.005 and 0.0005 mg. (between 5 and 0.5 μg).

2. A minimal dose of 0.0005 mg. (0.5 μg) given daily would probably prevent the development of hemorrhagic disease with the exception of the few cases that occur within the first twenty-four hours.

3. Approximately 1.25 mg. of the test substance is apparently effective in lowering an excessively high prothrombin time to a normal range and maintaining it in this range without further medication.

4. The administration of seconal, nembutal, and sodium amytal to the mothers of the babies studied in this series had no demonstrable effect in prolonging the prothrombin time of the babies.

5. Synkayvite, given in the doses and concentrations mentioned, does not produce vomiting in the newborn infant.

This study was suggested by Dr. Henrik Dam, and I should like to express my appreciation of the valuable advice and criticism given me by both Dr. Dam and Dr. Samuel Clausen throughout this work.

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HISTOPLASMOSIS

Report of a Case in an Infant and Experimental Observations

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St. Louis, Mo.

DARLING,[1] in 1906, working in the Panama Canal Zone, noticed a relatively large, unicellular, encapsulated microorganism occurring intracellularly in the tissues of a man who died of a generalized infectious disease which resembled kala-azar clinically. The same year a similar organism was noted by Strong[2] in curettings from an abscess of the chest in a native woman of the Philippine Islands. Two years later Darling[3] reported two additional fatal cases which were similar to his first one. Study of tissues obtained from the three cases at autopsy led him to conclude that the etiologic agent, which he named *Histoplasma capsulatum*, was a protozoon resembling Leishman-Donovan bodies but differing in certain morphologic characteristics such as the shapes and positions of the nuclei and the absence of rod-shaped kinetoplasts.[4] A few years later Rocha Lima (1912) suggested that *Histoplasma capsulatum* was a fungus closely related to *Cryptococcus farciminosus*, the etiologic agent of infectious lymphangitis in horses. DeMonbreun,[37] in 1934, was the first to culture the organism on artificial media and showed that it was a fungus exhibiting two phases of growth, one a yeastlike form, as seen in the tissues, and the second, a mycelial, sporulating form usually found in cultures incubated at temperatures lower than 37° C.

Following Darling's studies in 1908, this disease was not reported again in medical literature until 1926, when Watson and Riley[5] reported generalized histoplasmosis in a woman who had resided in Minnesota for forty-two years and Phelps and Mallory[6] reported histoplasmosis of the lungs in a Honduran man who had a primary carcinoma of the liver.

Since that time there have been thirty-one additional cases described by several authors[7-35] and twelve unpublished cases cited by Meleney.[36] In addition to the cases mentioned above, we know of four diagnosed in St. Louis,* but not yet mentioned in the literature. Of this total of fifty-three cases, all were found in the United States except eleven, of which three occurred in Panama, two in the Philippine Islands, two in South America, and one each in Honduras, East Java, England, and South Africa. In the United States the disease is apparently widespread, cases having been found in California, District of Columbia, Minnesota, Alabama, Missouri, Florida, Tennessee, Michigan, Virginia,

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*The authors are indebted to Dr. Morris Moore, Mycologist at the Barnard Free Skin and Cancer Hospital, St. Louis, Mo., for information concerning these cases.

Kentucky, Iowa, Illinois, Ohio, and Maryland. Nine cases[10-13, 22-24, 29, 34] were diagnosed in infants less than 15 months of age. DeMonbreun,[38] in 1939, from a biopsy of the liver of a dog, diagnosed the only case of histoplasmosis which has been seen in animals as a natural infection.

This present report is the fiftieth recorded case of histoplasmosis in human beings, the tenth to occur in an infant less than 15 months of age. Observations made in this study, and others in the literature, indicate that the disease may be diagnosed by routine blood cultures, blood smears, or examination of sternal bone marrow. Careful and adequate examination of blood cultures may reveal growth as early as the third or fourth day following inoculation of the medium. This is much earlier than incubation periods generally recorded in the literature.

CASE REPORT

History and Clinical Course.—The patient, a 10½-month-old white, male infant, was admitted to St. Louis Children's Hospital on June 26, 1942, because of an acute illness of one week's duration characterized by fever, cough, and difficult respiration. Since 4 days of age the patient had lesions of the skin which were diagnosed as impetigo and treated with soap and water and ammoniated mercury ointment. The lesions varied in number and severity under this treatment but apparently were constantly present. At the time of onset of acute symptoms, another physician treated the skin lesions by breaking the vesicles, cleansing with alcohol, and applying mercurochrome. About four days before admission an abscess developed at the right anterior nasal orifice, obstructing the nasal passage and producing swelling of the adjacent portion of the face. The abscess apparently ruptured spontaneously two days before the child entered the hospital. There was no history of vomiting or diarrhea.

The patient was born in a hospital by normal delivery at full term. He was breast fed until 9 months of age. During this time he received the usual dietary additions, including vitamins, and he gained regularly. He then received pasteurized, whole cow's milk and continued to do well until one week before admission. The infant had frequent upper respiratory tract infections associated with cough during the preceding winter months but had no serious febrile illnesses. He was the only child of young parents, and the mother was in good health during and following the pregnancy. The remainder of the family history contributed no relevant facts.

Physical examination revealed an acutely ill infant whose general nutrition and development were fairly good. The rectal temperature was 39.6° C. He presented the picture of profound sepsis and was semicomatose except for periods of marked irritability and restlessness. The skin was dry and the conjunctivae were glassy. Generalized skin lesions, most concentrated on the trunk, were covered with the stain of mercurochrome; these lesions were intact, ruptured, or encrusted vesicles. The vesicular fluid was cloudy, and cleansing left a red area. Most of the lesions were from 2 to 3 mm. in diameter. There were numerous petechiae on the extremities. Cyanosis of the mucous membranes was observed. The respirations were irregular and grunting in character. There was a persistent, moist cough. The mucous membranes of the pharynx and nose were red. The nasal passages were unobstructed, but there was considerable crusting in the right nostril. The adjacent skin was wrinkled and discolored. The eardrums were reddened. The lungs were clear to percussion, breath sounds were roughened, but no râles were heard. The rate of the heart was rapid and the tones were weak, but

no murmurs were heard. Fluoroscopic examination of the chest showed no definite areas of increased density in the lung fields; the heart was small and in normal position. The diaphragm moved normally. The abdomen was rounded and soft. The liver was palpable 2 cm. below the right costal margin, and the spleen was definitely enlarged. As far as could be determined the reflexes and extremities were normal. There was questionable stiffness of the neck and spine.

Laboratory Data.—The blood contained 3,600,000 erythrocytes and 16,000 leucocytes per cubic millimeter and 6.7 Gm. of hemoglobin per 100 c.c. A differential count showed 1 per cent eosinophiles, 25 per cent "juveniles," 55 per cent "stab" forms, 6 per cent segmented polymorphonuclear leucocytes, 10 per cent lymphocytes, and 3 per cent monocytes. No urine was collected. The Kline reaction of the blood serum was negative. Spinal fluid obtained by lumbar puncture was clear and contained 4 lymphocytes per cubic millimeter; the Pandy test was negative. No organisms were seen in the smear and the culture was sterile. Chemical examination of the blood showed the following: serum carbon dioxide content, 48.0 volumes per cent; serum nonprotein nitrogen, 35.5 mg. per 100 c.c.; serum chlorides (as sodium chloride), 540 mg. per 100 c.c.; and serum true glucose, 86.0 mg. per 100 c.c. A throat culture and a blood culture were both reported to show hemolytic *Staphylococcus aureus.*

The clinical impression was that the infant had an overwhelming septicemia. The relation of the skin lesions to the general picture was not clear, except that they were possibly a portal of entry for the organism. Although obscured by medication, the lesions appeared to be impetigo.

The infant was given 180 c.c. of 10 per cent dextrose intravenously, followed by 16 c.c. of 5 per cent sodium sulfadiazine intravenously and 400 c.c. of Ringer's solution subcutaneously. Nine and one-half hours after admission the patient was given a second intravenous injection of 16 c.c. of 5 per cent sodium sulfadiazine with an additional infusion of 400 c.c. of Ringer's solution. The infant's condition became steadily worse. Inhalations of 5 per cent carbon dioxide and 95 per cent oxygen brought about no improvement. The rectal temperature was about 39.0° C. until death occurred thirteen and one-half hours after admission.

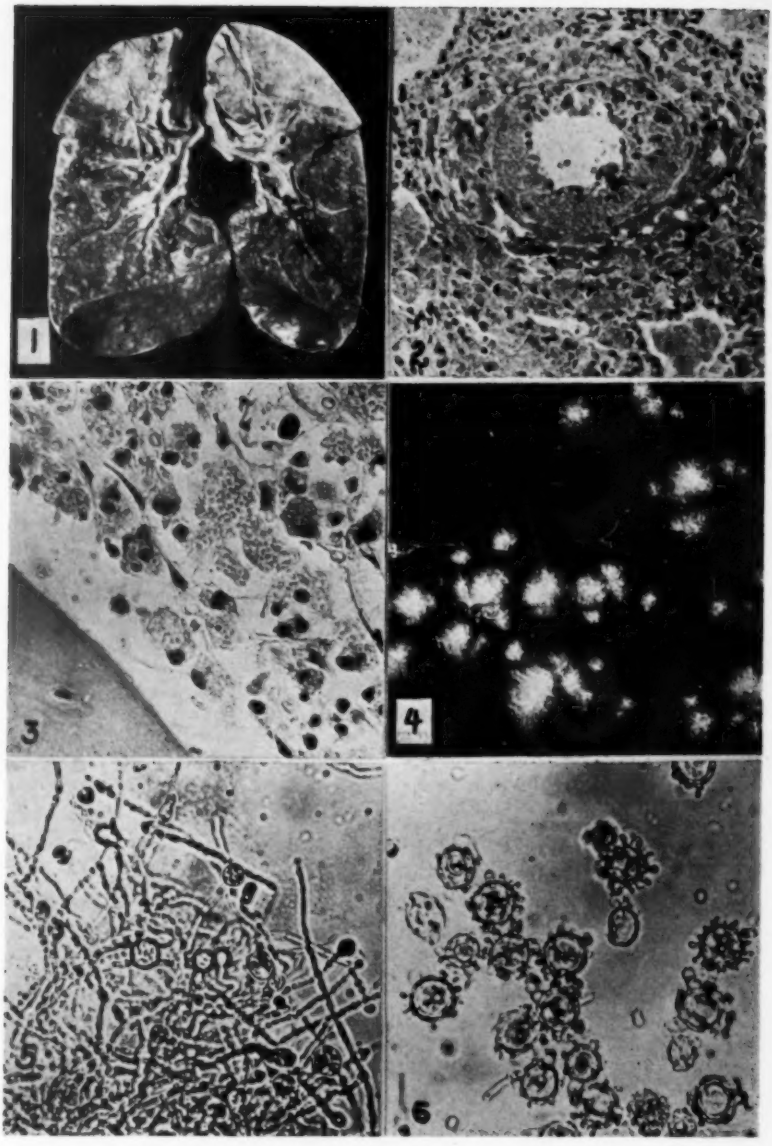
Autopsy.—Permission was granted for examination of the thorax and abdomen. The autopsy was performed three and one-half hours after death. Around the right nasal orifice the skin and mucous membranes were dry and crusted. The skin of the head, back, and left lower extremity showed several round areas of superficial ulceration varying from 1 to 3 cm. in diameter. The areas were discolored red by medication. On the arms, legs, and trunk were numerous scattered petechiae. Distributed throughout the pulmonary parenchyma were many irregular, poorly defined, moderately firm, dull yellow-gray masses varying from 1 to 10 mm. in diameter (Fig. 1). The hilar, mediastinal, periaortic, peripancreatic, mesenteric, and omental lymph nodes were enlarged to twice normal size. In each lymph node were several poorly defined, irregular, yellow-gray foci. In the liver, spleen, and kidneys there were a few moderately firm, gray, spherical masses from 1 to 2 mm. in diameter. The liver weighed 355 Gm. and the spleen weighed 75 Gm. The pleurae, pericardium, and peritoneum were normal except for several hemispherical, moderately firm, gray masses, from 1 to 3 mm., beneath the peritoneum of the left leaf of the diaphragm. The mucosa of the appendix, cecum, and entire colon was studded with slightly elevated, soft, gray masses of necrotic tissue. Beneath the masses the superficial mucosa was absent. Grossly, the bone marrow of the sternum, ribs, and vertebrae was pale but not otherwise unusual. The thymus, heart, aorta, pancreas, adrenals, ureters, prostate, seminal vesicles, testes, esophagus, stomach, and small intestine were grossly normal.

Microscopically the lungs showed collections of large phagocytic cells in the alveoli, in the alveolar walls, and involving the walls of the bronchi and arteries (Fig. 2). The cells were engorged with *Histoplasma capsulatum,* which appeared as

round bodies, from 2 to 4 μ in diameter, with clear centers and a rim of dense chromatin. Several small arteries were obliterated by masses of phagocytic cells containing the organisms. There were masses of similar cells in the lymph nodes, located predominantly in the sinusoids. The general architecture of the lymph nodes was preserved, and the lymphoid follicles were small and intact. The Kupffer cells of the liver were enlarged and contained many of the yeastlike bodies. The spleen was similar to the lymph nodes except that several blood sinuses also contained monocytic cells filled with *Histoplasma capsulatum*. The masses beneath the diaphragmatic peritoneum were composed of engorged phagocytes. In the pancreas were two microscopic foci of engorged phagocytic cells around interlobular blood vessels. In the cortices of the adrenal glands there were similar microscopic foci except that a few of the cells containing organisms were glandular cells of the adrenal cortex. Numerous areas in the interstitium of the kidneys were involved by engorged phagocytic cells which compressed the surrounding glomeruli and tubules. Portions of superficial mucosa of the appendix, cecum, and colon were necrotic and ulcerated. The necrotic portions contained interweaving, branching hyphae about 1 μ in diameter with bulbous enlargements at intervals and at the tips. These were interpreted as probably being *Histoplasma capsulatum*. In the interstitium of the mucosa beneath the ulcers were scattered phagocytic cells containing yeastlike forms of the organism, and in the submucosa beneath the ulcers were swollen masses of such cells. The bone marrow of the sternum, ribs, and vertebrae was composed predominantly of large phagocytes containing *Histoplasma capsulatum* (Fig. 3). No necrosis was present in any of the tissues except in the mucosa of the intestine and one small focus in a mediastinal lymph node. In the center of the necrotic focus in the node were colonies of gram-positive cocci. In the tissues generally there was a lack of any type of inflammatory reaction except the proliferation of cells of the reticulo-endothelial system. Monocytic cells containing many organisms were found free in the blood vessels of the heart, spleen, kidneys, prostate, colon, and bone marrow. No lesions were present in the heart, gall bladder, bile ducts, ureters, prostate, seminal vesicles, testes, stomach, small intestine, muscle of the diaphragm, or skin from the thorax anteriorly.

DIAGNOSTIC AND EXPERIMENTAL MYCOLOGIC STUDIES

At autopsy specimens of blood were collected aseptically from the heart. Approximately 5 c.c. were inoculated into 30 c.c. of glucose-tryptose broth and 1 c.c. was placed in a sterile Kolmer tube. Owing to the obscure nature of the illness, pieces of the lung, liver, and spleen were taken aseptically and placed in sterile tubes which were subsequently sealed and stored in a solid carbon-dioxide-alcohol mixture. The large tube of glucose-tryptose broth, inoculated with the patient's blood, was incubated aerobically at 37° C. Blood from the sterile Kolmer tube was streaked on three plates of 5 per cent rabbit blood infusion agar. Two of these were incubated at 37° C. aerobically and anaerobically and the third was incubated aerobically at room temperature (from 25 to 28° C.). Swabs from lesions in the liver and the spleen also were streaked on blood agar plates and incubated aerobically and anaerobically at 37° C. The latter cultures were positive for hemolytic *Staph. aureus* after two days. Examination after ten days yielded no additional results from these cultures which, by then, had "heavy" growths of staphylococci. On the fourth day following inoculation the blood agar plate streaked with a loopful of the patient's blood and incubated aerobically at room



Figs. 1-6.

Fig. 1.—Lungs, showing numerous, irregular, poorly defined, moderately firm, dull yellow-gray masses varying from 1 to 10 mm. in diameter.

Fig. 2.—Lung. Note organisms within phagocytic cells in the alveoli and alveolar walls and in the wall of the blood vessel (×135).

Fig. 3.—Vertebral bone marrow showing large macrophages containing numerous yeastlike forms of *Histoplasma capsulatum* (×470).

Fig. 4.—Colonies of *Histoplasma capsulatum* on blood agar plate incubated at room temperature for four days (×6; photographed with transmitted light).

Fig. 5.—Water mount of a portion of a colony shown in Fig. 4 (×570).

Fig. 6.—Water mount from a culture (from eleven to twelve days old) showing tuberculate asci (×570).

temperature showed growth which did not appear to be bacterial colonies. These were innumerable, irregular, gray-white colonies, 1 mm. in diameter, with opaque, rough centers and filamentous edges, blending with the color of the medium (Fig. 4). They were best seen with transmitted light. Under direct examination with a magnification of 35× there were observed small, almost continuous colonies, each composed of many submerged, and a few aerial, hyphae forming occasional racquet mycelia. From one of these colonies, which were tenacious and firmly adherent to the medium, a water mount was prepared (Fig. 5). The hyphae were from 1.5 to 2.5 μ in diameter, septate, and multinucleate; they contained intercalary, lateral, and terminal chlamydospores from 2 to 9 μ in diameter. The terminal chlamydospores, measuring from 10 to 12 μ in diameter, tended to be larger than the others. The organism was tentatively identified as *Histoplasma capsulatum*, and this was confirmed by subsequent examinations. On the eighth and ninth days a few tuberculate asci were observed on aerial hyphae. Two to three days later the asci were more prominent (Fig. 6). At this time the blood-glucose-tryptose broth showed many yeastlike forms of the organism, from 2 to 3 μ in the long diameter, resembling closely those described by DeMonbreun,[34] who first cultured this organism in its two growth phases from blood and tissues. Small colonies of the yeastlike phase were found also on the blood agar plates incubated at 37° C.

Tissues, sealed and frozen in sterile tubes at the time of autopsy, were thawed and ground with sterile sand in physiologic salt solution. The resulting suspension was inoculated onto Sabouraud's and blood agar slants which were incubated at room temperature and at 37° C. The blood agar cultures revealed growth in from four to five days, and the cultures on Sabouraud's agar were positive on the sixth day. The mycelial form of the fungus was prevalent on blood agar incubated at room temperature and on Sabouraud's agar incubated either at room temperature or at 37° C. Further studies showed that the growth and reactions of the organism in sugar media, litmus milk, and gelatin were identical with those described for the species.[40]

During the course of these studies smears were prepared from the blood collected at autopsy and stored for several weeks in the refrigerator (from 5 to 8° C.) in a nonsterile, corked Kolmer tube. Mononuclear cells contained intracellular yeastlike forms. Several partly disintegrated leucocytes contained a few organisms, some of which were protruding from the cytoplasm and others which were free at the periphery of the cell. Throughout the smear there were numerous extracellular, heavily encapsulated, slightly larger, yeastlike forms, but no hyphae or mycelial structures were observed. It is at least reasonable to believe that these were truly extracellular forms of the fungus since (1) the organism did not grow when incubated at from 5 to 8° C. and (2) the free yeastlike cells were larger and more thickly encapsulated than those seen intracellularly. The observation of these

extracellular forms confirms the report of Rhodes, Conant, and Glesne,[23] who first observed similar organisms in tissue impression slides made from the liver at the time of autopsy.

Approximately 3 Gm. of spleen removed aseptically at autopsy were ground with sterile sand in a sterile mortar and suspended in 6 c.c. of sterile physiologic salt solution. Varying amounts of this suspension (from 0.3 to 0.5 c.c.) were inoculated intraperitoneally into six mice about 5 months of age. Of this group two developed histoplasmosis involving the spleen, liver, and lungs. The other four, when sacrificed 120 days after inoculation, showed no significant pathologic changes. Further experiments with mice indicated that young mice, averaging from 1 to 2 months in age, are infected with more regularity than are the older ones. This procedure probably is not as reliable as cultures in establishing the presence of the organisms in tissues.

Experiments were performed to determine the resistance of *Histoplasma capsulatum* under different conditions. Several blood agar and Sabouraud's maltose agar plates were seeded heavily with growth from a six-day culture on blood agar. These plates were then incubated at from 5 to 8° C. for several weeks, plates being removed at intervals and examined. After fourteen weeks there was no growth as determined by macroscopic and microscopic examinations. However, the organisms were viable during this period as evidenced by profuse growths on these same plates when removed from the refrigerator and incubated at room temperature. Glucose-tryptose broth cultures of the organism incubated at room temperature for from twenty-four to thirty days were used to inoculate sterile, glass beads and sterile soil placed in several sterile tubes. These were then allowed to dry at room temperature. At monthly intervals sterile broth was added to some of the tubes and allowed to incubate at room temperature. It was found that *Histoplasma capsulatum* could remain viable as long as four months under these conditions.

The fact that this child was fed pasteurized milk, together with the presence of lesions in the intestinal tract, raised a question concerning the ability of the organism to withstand pasteurization temperatures. Large inocula of broth cultures of the organism were placed in small tubes of sterile broth and in whole milk. These tubes were heated at from 62 to 63° C. for ninety minutes, one tube of each medium being removed every ten minutes and subcultured. No growth was obtained from any of the broth tubes, but the organism was viable for at least ten minutes in milk heated at from 62 to 63° C.

It was felt that a deficiency of ascorbic acid in the diet might be a factor in the establishment of the organism in the intestinal tract, from which focus it might produce a generalized systemic infection. One cubic centimeter of a broth culture of the organism was fed to apparently normal, young guinea pigs and also to vitamin C-deficient ani-

mals on each of four successive days. Following these feedings both groups were maintained on a normal diet. None of the animals developed histoplasmosis nor was the organism isolated from the feces.

DISCUSSION

Histoplasmosis is a subacute or chronic, highly fatal, infectious disease caused by an intracellular, yeastlike organism, *Histoplasma capsulatum*. The disease occurs in all age groups and in both sexes, although in adults the incidence in men is about five times greater than in women. Of the nine cases reported in infants, four have occurred in the male sex. The majority of cases have been reported since 1939, but it is difficult to say whether this is a true increase in incidence or increased recognition. The occurrence of cases in widely separated regions within the United States and in Africa, South America, East Java, England, and the Philippine Islands suggests that the distribution is worldwide. During the past four years nine cases, besides the present one, were diagnosed in St. Louis, six of which were in residents of St. Louis or St. Louis County. The others occurred sporadically in rural areas in Missouri and Illinois (Fig. 7).

Fig. 7.—Outline map of Missouri and Illinois showing residences of ten patients with histoplasmosis diagnosed in St. Louis in the past four years.

Thus far, investigators have been unable to determine definitely the mode of transmission and the route of infection. Frequency of pulmonary involvement suggests the respiratory tract as the route of infection, but Henderson and his associates[28] failed to infect guinea pigs and dogs by intratracheal injections of cultures. In at least nine human cases oral and intestinal lesions were found, and, experimen-

tally, dogs may be infected by the oral route. However, in the present study attempts to infect guinea pigs by feeding cultures were unsuccessful. The possibility of transmission by insects should be considered since intracellular yeasts are known to occur in insects. In one case[34] a large, black ant was seen on an infant shortly before an acute illness which terminated in death due to generalized histoplasmosis. Attempts to solve the problem of mode of transmission in the present case were unsuccessful. Whether or not the skin lesion was the site of entry of the organism is not certain, since no attempt was made to isolate the organism from this site and the skin of this region could not be examined at autopsy.

Depending on the dominant clinical picture, histoplasmosis may be classified into several types; for example, generalized, pulmonary, intestinal, naso-oral, cutaneous, and joint types.[39] Recently a case of vegetative endocarditis due to *Histoplasma capsulatum* was reported,[35] and we know of a similar, unpublished case which was diagnosed in this laboratory. In nearly all the cases of histoplasmosis in infants there is generalized involvement. Usually there is an insidious onset and the illness is characterized by failure to gain weight or loss of weight, anorexia, weakness, and fever. Symptoms suggesting infection of the upper respiratory tract, diarrhea, and vomiting are prominent features in several of the reported cases in infants. Almost constantly there is enlargement of the spleen and liver with anemia and leucopenia. Frequently, however, there is leucocytosis owing to the presence of other infection.

The clinical diagnosis of histoplasmosis has been made during life in less than twelve cases. In other instances the diagnoses were made from post-mortem material or from ante-mortem specimens examined after the death of the patient. Frequently, although blood was cultured ante mortem, growth was not observed until from twelve to thirty days later, perhaps after the patient died. Except for a few instances, blood cultures did not facilitate a diagnosis before death. If examined adequately, however, positive cultures probably could be determined much earlier. For example, in two instances in this laboratory, growth of *Histoplasma capsulatum* on blood agar plates was detected as early as the fourth day by the use of a simple, hand lens. Furthermore, in any cases of obscure nature in which the patients present the general symptoms and signs mentioned above, blood cultures or cultures made from biopsies should be observed frequently over a period of several days in the event that growth of the organism would occur more slowly.

The diagnosis may be made also by careful examination of blood films and biopsies of bone marrow, lymph nodes, skin, and other tissue. In several instances the yeastlike, intracellular parasites were observed ante mortem in phagocytic cells of the bone marrow or peripheral blood and, in others, re-examination of ante-mortem blood films, once

the diagnosis was established at autopsy, revealed the organisms in the peripheral blood cells, especially the monocytes. Recently[35] a case of histoplasmosis was diagnosed from a biopsy of liver taken during a laparotomy.

SUMMARY

1. A case of generalized histoplasmosis in a male infant, 11 months of age, with autopsy, mycologic, and experimental studies is reported. Lesions were found in the lungs, liver, spleen, adrenal glands, kidneys, colon, appendix, bone marrow, lymph nodes, and blood vessels.

2. Macroscopically visible colonies of *Histoplasma capsulatum* were observed on blood agar plates (incubated aerobically at room temperature) on the fourth day following inoculation with blood taken from the heart at autopsy.

3. Yeast like forms of the fungus were observed in blood films prepared post mortem.

4. Experiments indicate that *Histoplasma capsulatum* is resistant to drying and to low temperatures (from 5 to 8° C.).

5. *Histoplasma capsulatum* is destroyed in milk by heating at from 62 to 63° C. for twenty minutes.

6. Infection of guinea pigs, normal and vitamin C deficient, could not be established by oral feedings with large numbers of organisms.

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IMMUNIZATION WITH COMBINED DIPHTHERIA AND TETANUS TOXOIDS (ALUMINUM HYDROXIDE ADSORBED) CONTAINING HEMOPHILUS PERTUSSIS VACCINE

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A PREVIOUS report[1] has described the results obtained in infants given diphtheria and tetanus toxoid concurrently with *H. pertussis* vaccine. Seventy-six children received fluid toxoids and *H. pertussis* vaccine, and 100 children received alum-precipitated toxoids and vaccine. The vaccine was not mixed with the toxoids but was injected in the opposite arm concurrently. The effectiveness of this procedure was measured in terms of Schick tests, tetanus antitoxin titrations, *H. pertussis* agglutination tests, and observations on the results of indoor exposures to whooping cough.

With alum-precipitated toxoid and pertussis vaccine given concurrently, satisfactory diphtheria and tetanus antitoxin production was obtained and serologic and clinical evidence of immunity to pertussis was demonstrated. With fluid toxoids and vaccine, less tetanus antitoxin production was noted, but the immune reactions to the diphtheria toxoid component and to the pertussis vaccine were quite satisfactory. It was therefore concluded that concurrent administration of the three antigens studied was as satisfactory as sequential administration.

Ramon[2] has advocated the simultaneous injections of three or more antigens for a number of years. Lapin[3, 4] and Daughtry-Denmark[5] have applied the principle to tetanus, diphtheria, and pertussis. Like theirs, this report deals with the administration of diphtheria and tetanus toxoids mixed with *H. pertussis* vaccine and injected as such. Aluminum hydroxide, rather than alum, however, was the adsorbent used.

Aluminum hydroxide-adsorbed diphtheria toxoid was first produced by Schmidt[6] in 1932. Leach, Jensen, and Pöch[7] used a single injection of 2.0 c.c. of this material to immunize 553 Austrian children against diphtheria. They reported that all of 148 children tested before and twenty-eight days after the injection showed an increase in antitoxin titer. Furthermore, clinical immunity was obtained. During the subsequent five months diphtheria occurred in a control group of children. The expected number of cases in the immunized group was twenty-two, but no cases occurred. A single injection of aluminum hydroxide-adsorbed toxoid was found by Jensen[8] to act as a continuous stimulus for "at least 3-5 weeks."

The product we used* was prepared from diphtheria toxins containing from 26 to 30 Lf units per cubic centimeter and tetanus toxins containing from 100,000 to 120,000 M.L.D. per cubic centimeter. After conversion into toxoids and adsorption with aluminum hydroxide, potency tests indicated that more than 2 units per cubic centimeter of both diphtheria and tetanus antitoxin were produced (in guinea pigs). In each cubic centimeter of the final product was incorporated 20 billion phase I *H. pertussis*.† The schedule of injection is given in Table I.

TABLE I

SCHEDULE OF IMMUNIZATION

1.	1.0 c.c. combined diphtheria and tetanus toxoids, aluminum hydroxide adsorbed, with 20 billion *H. pertussis*
	12-Week Interval
2.	1.0 c.c. of the same
	4-Week Interval
3.	Smallpox vaccination
	8-Week Interval
4.	Schick test

The total dose of 40 billion *H. pertussis* per cubic centimeter was lower than that usually advocated. However, in view of the encouraging results reported by Bell[9] with a total of 20 billion and by Kendrick[10] with a total of 30 billion *H. pertussis* adsorbed on alum, it was felt that 40 billion *H. pertussis* adsorbed on aluminum hydroxide might be sufficient.

METHODS

The tetanus antitoxin titrations were carried out in mice according to the technique of Glenny and Stevens.[11] The test dose of toxin‡ routinely used was that which, when mixed with 0.001 American unit of standard tetanus antitoxin,§ killed mice in from seventy-two to ninety-six hours. The use of this small amount of toxin enabled us to titrate small volumes of sera which could be obtained by an ear or heel puncture. The blood was collected in Lyon's tubes. Frequent repeated bleedings were thus facilitated, although low levels of antitoxin could not be determined. (The less serum available, the higher the minimum titer that can be determined.)

Schick tests controlled with heated toxin‖ determined the antigenicity of the diphtheria toxoid used.

The antigenicity of the pertussis vaccine used was ascertained by an agglutinative reaction developed in this laboratory[12] and was also gauged by the results of a few exposures which are recorded.

*Kindly supplied by the Cutter Laboratories, Berkeley, Calif.

†The mixture is hereafter referred to in this paper as AADTP.

‡Kindly supplied us in a dried state by Mr. F. G. Jones of Eli Lilly and Co., Indianapolis, Ind.

§Kindly supplied us by Dr. M. V. Veldee, Chief of the Division of Biological Control, National Institute of Health.

‖The Schick test toxin and control was that of Eli Lilly and Co., Indianapolis, Ind.

AGE DISTRIBUTION

The age distribution of the children studied is recorded in Table II.

TABLE II

AGE DISTRIBUTION

AGE	NUMBER OF CHILDREN
Less than 6 months	7
6 to 12 months	110
13 to 24 months	18
2 to 3 years	7
3 to 4 years	8
4 to 5 years	8
5 to 6 years	6
Greater than 6 years	8
Total number	172

RESULTS OF TETANUS ANTITOXIN TITRATIONS

The results of the titrations of sera for tetanus antitoxin are shown in Table III. There it will be observed that unusually high titers of antitoxin were produced and persisted for one year.

After one injection only, all of nineteen children tested exhibited antitoxin. At from three to four weeks after the second injection all of sixty-five children tested had more than 1 unit of antitoxin per cubic centimeter and eighteen exhibited more than 10 units. At three months after the second injection seventeen of twenty children had more than 1 unit. At six months, twenty-four of thirty-seven children had more than 1 unit. At nine months, twenty-five of thirty-two children were above 1 unit, and at one year, sixteen of twenty-eight children exhibited more than 1 unit.

Furthermore, only one child showed a decrease in titer below 0.1 unit per cubic centimeter—the level generally conceded to be protective. (The usual prophylactic dose of tetanus antitoxin results in the transient presence of from 0.1 to 0.5 unit of antitoxin per cubic centimeter.[13, 14, 15])

A year after the second injection, twenty-six children were reinjected with 0.5 c.c. of AADTP. As noted in Table III, all of them at the time of reinjection exhibited titers of 0.1 unit or more. Of thirteen children tested from four to six days later, all were found to have titers of 1.0 unit or more. Sera were also obtained from thirteen children from four to six weeks after the 0.5 c.c. reinjection, and all children exhibited titers of 10.0 units or more.

DISCUSSION OF TETANUS ANTITOXIN TITRATIONS

The almost uniform production of high levels of tetanus antitoxin following two injections of AADTP and the prolonged maintenance of these high levels indicate that this is an excellent antigen for im-

TABLE III

TETANUS ANTITOXIN TITERS

307 TESTS ON 149 CHILDREN

ANTITOXIN TITERS	NUMBER OF SERA TESTED													
APPROXIMATE TITER KNOWN (UNITS)	AT SECOND INJECTION	THREE TO FIVE DAYS AFTER SECOND INJECTION	ONE WEEK AFTER SECOND INJECTION	THREE TO FOUR WEEKS AFTER SECOND INJECTION	IN INTERIM BETWEEN ↙ ↘	TWELVE TO FOURTEEN WEEKS AFTER SECOND INJECTION	IN INTERIM BETWEEN ↙ ↘	±SIX MONTHS	IN INTERIM BETWEEN ↙ ↘	±NINE MONTHS	IN INTERIM BETWEEN ↙ ↘	±ONE YEAR AT THIRD INJECTION*	FOUR TO SIX DAYS AFTER THIRD INJECTION	FOUR TO SIX WEEKS AFTER THIRD INJECTION
0.01 or more but < 0.05										1				
0.05 or more but < 0.1	2							1						
0.1 or more but < 0.5	6	1				1	1	2	1			4		
0.5 or more but < 1.0	8	4			2	2	3	10	1	6	2	8		
1.0 or more but < 5.0	3			16	11	12	20	22	7	24	1	15	6	
5.0 or more but < 10.0		1	1	31	12	5	5	2	1	1		1	3	
10.0 or more				18	5		1						4	13
Totals														
Number of sera 0.1 unit or more	17	6	1	65	30	20	30	36	10	31	3	28	13	13
Number of sera < 0.1 unit	2	0	0	0	0	0	0	1	0	1	0	0	0	0
Number of sera 1.0 unit or more	3	1	1	65	28	17	26	24	8	25	1	16	13	13
Number of sera < 1.0 unit	16	5	0	0	2	3	4	13	2	7	2	12	0	0
Total number sera tested	19	6	1	65	30	20	30	37	10	32	3	28	13	13

*Two children were not reinjected.

munization against tetanus. Furthermore, after a yearly reinjection of 0.5 c.c. of AADTP the titers increased considerably.

We are not aware of any report describing the persistence of levels of this height for one year after an initial course of tetanus toxoid. Maintenance of concentrations of antitoxin over 0.1 unit per cubic centimeter for one year has been reported[13, 16, 17, 18] following a course of three injections of alum-precipitated toxoid. In our own experience[19] three injections of alum toxoid, at three-month intervals, resulted in the maintenance for one year of levels over 0.1 unit in thirty-eight of forty-two children followed. (Two injections of alum toxoid did not result in such uniform maintenance of titer.) In the present report, which is strictly comparable, all of twenty-eight children tested have levels in excess of 0.1 unit at one year, and sixteen have levels in excess of 1.0 unit.

The desirability of securing and maintaining in the blood high concentrations of tetanus antitoxin has been discussed.[1, 19, 20] We feel that in pediatrics tetanus immunization should imply complete protection—the continued presence of antitoxin in concentration as high as can be attained transiently by prophylactic antitoxin. Booster injections at the time of trauma should always be given but unfortunately are not always given.

RESULTS OF SCHICK TESTS

Schick tests were performed on 114 children at approximately six months after the second AADTP injection. All of these children showed Schick-negative reactions. The results of this type of immunization to diphtheria are, therefore, highly satisfactory.

RESULTS OF PERTUSSIS AGGLUTINATIVE TESTS

The bacterial antibody produced in the group of infants and children studied is charted in Table IV. It will be observed that the majority of children produced agglutinins in high titer. However, several children had extremely low titers, and others showed a marked decrease in titer over a period of one year following the second AADTP. It is interesting to note that one child's titer increased from 1:40 at thirty-three weeks after the second AADTP to 1:640 at one year.

These data are directly comparable to those presented in previous papers.[1, 12, 21, 22] Following injection of 80 billion *H. pertussis* in divided doses within a period of one month, we observed[21] the production of agglutinins in all but five of 215 children. The titers attained in from two to four months after completion of the vaccine remained relatively constant thereafter. With few exceptions no tendency to decline from this "plateau" was observed during the subsequent six years. The mean level of agglutinins was between the titers of 1:320 and 1:640.

In the present study, where two doses of 20 billion *H. pertussis* were administered with twelve weeks between, much more marked variabil-

TABLE IV

PERTUSSIS AGGLUTINATIVE TITERS

219 TESTS ON 121 CHILDREN

AGGLUTINATIVE TITERS	NUMBER OF SERA TESTED												
	AT SECOND INJECTION	THREE TO FIVE DAYS AFTER SECOND INJECTION	ONE WEEK AFTER SECOND INJECTION	THREE TO FOUR WEEKS AFTER SECOND INJECTION	FIVE TO EIGHT WEEKS AFTER SECOND INJECTION	TWELVE TO FOURTEEN WEEKS AFTER SECOND INJECTION	IN INTERIM BETWEEN ↙ ↘	± SIX MONTHS	IN INTERIM BETWEEN ↙ ↘	± NINE MONTHS	IN INTERIM BETWEEN ↙ ↘	± ONE YEAR AT THIRD INJECTION	FOUR TO SIX WEEKS AFTER THIRD INJECTION
1:2560		1	1	24	9	6	1	12	1	3		7	8
1:1280	1			7		3	4	8	1	13		3	3
1:640	2			1	2	2	2	7		3		6	
1:320				5	2	3		4	1	3			1
1:160	2				1	2		2		3		2	
1:80	1	1		1	1		3	7		4		3	
1:40	3							2	1	4		1	
1:20	1							1		1		1	
1:10							1			1			
Negative at 1:20		2		1					1	1		2	
Negative at 1:10					2								
Total	10	4	1	39	17	16	11	43	5	36		25	12

ity in agglutinin production was observed. Whereas ten of twenty-five sera tested at one year were positive in dilutions of 1:1280 or higher, nine sera were positive in dilutions of only 1:160 or lower. Of these nine, five sera exhibited agglutinins in dilutions of only 1:40 or lower. From four to six weeks following a 0.5 c.c. reinjection one year after the second AADTP, eleven of twelve children tested showed high titers of 1:1280 or more.

The results were similar to those we reported[21] when 50 billion *H. pertussis* suspended in saline were used. It would seem, therefore, that so far as agglutinin production is concerned, the addition of aluminum hydroxide did not compensate for the decreased number of *H. pertussis* injected.

Considerable reliance is placed by us on the results of the agglutinative reaction as a measure of potency and a guide to immunization. Our view is not widely held; it is, however, based on clinical observation. For four years the agglutination titers of a large group of children were followed and the results of the indoor exposures to whooping cough were observed.[22] Eighty-three exposures occurred, twelve of which resulted in cases of whooping cough. (These figures include the four exposures added in the note at the end of the paper.[22]) Among the seventy-one children who escaped, the last agglutinative titers prior to exposure varied from 0 to 1:2560. Among the twelve children who were attacked, the pre-exposure titers varied from 0 to 1:160. These observations suggested that, whereas immunity may exist in the absence of demonstrable agglutinins, susceptibility does not occur in the presence of agglutinins in high titer.

With this experience as a backlog, the agglutinative reactions obtained in the children receiving AADTP do not appear satisfactory. The dose of 40 billion *H. pertussis* failed to lift the desired 90 per cent of the sera over the 1:320 agglutinin titer level. Forty billion *H. pertussis* may be sufficient for many children but not for 90 per cent of them, which would seem to be the maximum obtainable with any dose.

To determine whether the children who produced little or no agglutinin likewise produced relatively low amounts of tetanus antitoxin, the poor reactors were classified (Table V).

TABLE V

LOW P.A.R.* ONLY	LOW TET. AT† ONLY	LOW P.A.R. AND TET. AT
16	2	3

*The children charted here as having low pertussis agglutination reactions (P.A.R.) are those who showed agglutinins in dilutions of 1:160 or lower.

†The low tetanus antitoxin (Tet. AT) producers are those who were never able to produce more than 0.5 unit.

RESULTS OF EXPOSURE TO WHOOPING COUGH

Unfortunately the data on exposure to whooping cough are extremely limited. There was only one case of exposure after completion of im-

munization, and this resulted in an escape. Five exposures occurred during the course of immunization, and of these, three resulted in escapes and two in cases of whooping cough. All exposures were indoor exposures of at least two hours' duration.

DISCUSSION

In a recent paper Lapin[4] has compared different schedules that have been used for immunization against diphtheria, tetanus, and pertussis. Sequential administration of the three antigens, concurrent administration of the antigens separately, and the administration of a mixture of the antigens was performed. Schick tests, diphtheria antitoxin titrations, tetanus antitoxin titrations, pertussis agglutination tests (rapid technique), and pertussis complement fixation tests were all performed three months after completion of the schedules. The conclusion reached was that "prophylaxis by three monthly injections of pertussis vaccine followed by two injections at two-month intervals of combined alum-precipitated diphtheria and tetanus toxoids is superior because of its antigenicity and also because of its freedom from reactions." This conclusion seems hardly justified in view of the fact that (1) only ten children were injected in this manner and (2) the tests were carried out only three months after completion of the course.

Lapin[4] has emphasized the danger of producing sterile abscesses when pertussis vaccine is mixed with alum toxoids. We are not in a position to comment on this point as aluminum hydroxide was the adsorbent used by us. In our group of 172 children who received two injections, no abscesses were noted.

Our studies lead us to the conclusion that simultaneous administration of diphtheria, tetanus, and pertussis antigens has no disadvantages as compared with sequential administration. On the contrary, it has the practical advantage of lessening the number of injections necessary. While the response to pertussis vaccine was not entirely satisfactory, we believe that this fault can be readily corrected either by increasing the numbers of *H. pertussis* in the AADTP mixture or by giving an extra dose of pertussis vaccine during the interval between AADTP injections.

We have been particularly impressed with the exceptionally high and enduring levels of tetanus antitoxin obtained with aluminum hydroxide adsorbed toxoid, as well as with the perfect score in the Schick tests. Aluminum hydroxide appears on the basis of our study to be distinctly superior to alum in the preparation of tetanus toxoid and perhaps of diphtheria toxoid as well.

CONCLUSIONS

In our previous study a simultaneous decrease in tetanus antitoxin and maintenance of pertussis agglutinins with the passage of one year

was noted. This maintenance of antibacterial antibody and progressive loss of antitoxin in the same children was surprising.

In the present study the reverse of this is noted. The injection of 40 billion *H. pertussis* did not result in the maintenance of high agglutinin titers. Decreases in titer were common within one year. At the same time, the aluminum hydroxide adsorbed tetanus toxoid resulted in surprisingly stable levels of antitoxin with little tendency to decrease. It is apparently superior to alum-precipitated toxoid as an immunizing agent.

The conclusion is obvious—two injections of aluminum hydroxide adsorbed diphtheria and tetanus toxoids with 20 billion *H. pertussis* vaccine produced satisfactory immune responses with respect to diphtheria and tetanus, but the dose of *H. pertussis* vaccine was below optimal. The addition of a dose of 30 billion *H. pertussis* vaccine halfway between the first and second injection would, therefore, seem advisable.

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TORANTIL (HISTAMINASE) IN URTICARIA FOLLOWING SERUM ADMINISTRATION

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BEST and McHenry,[1] in 1930, reported that histaminase could be neutralized in vitro by a substance extracted from certain viscera, particularly the gastrointestinal tract and kidney. Since this substance displayed the properties of an enzyme, they called it histaminase. They prepared it as a stable powder and defined 1 unit as the amount necessary to neutralize 1 mg. of histamine after twenty-four hours of incubation at 37° C. at a pH of 7.2. Histaminase was subsequently manufactured for clinical use from porcine gastrointestinal tract. It was given the trade name of Torantil and distributed in the form of tablets or capsules, each containing 5 units.

It has been frequently suggested that a sudden release of histamine might be the mechanism whereby the various clinical signs of an allergic state are produced. Were this true, it would be logical to assume that a substance capable of destroying histamine in the body might be of therapeutic value. A number of investigators have, therefore, tested histaminase experimentally and clinically in a wide variety of conditions. The results have been diverse and difficult to interpret.

The only reports pertinent to our work were those concerned with use of histaminase in serum sickness after antitoxin or antiserum administration. Foshay and Hagebusch[2] reported "marked relief in twenty of twenty-two cases," with prevention of serum sickness in six of eight patients treated prophylactically. Roth and Horten[3] noted relief in from twelve to thirty-six hours in fourteen of seventeen patients; and Vaisberg[4] had good results in one patient. Cherry and Prickman[5] used Torantil to prevent and treat serum sickness in twenty-two patients with good results.

Many patients treated with serums and antitoxins develop serum sickness. It was decided to note the effect of Torantil in such patients in the Division of Contagious Diseases, City Hospital, Cleveland, following the administration of scarlet fever antitoxin, diphtheria antitoxin, pneumococcus antiserum or meningococcus antitoxin.

In the first clinical experiment, thirteen patients who developed urticaria were given four tablets of Torantil four times a day until the serum sickness had subsided. This procedure seemed worthless, since

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by any standard of comparison, the thirteen treated seemed no better than the thirteen untreated control patients. It was thought at the time that the amount of Torantil given had been inadequate.

In the next clinical experiment, 10 patients with urticaria were given six Torantil tablets four times a day for as long as ten days. When infants were to be treated, the tablets were crushed and placed in the formula. At no time was the medication administered parenterally. Again our results, when compared with ten untreated control patients, were inconclusive.

Our third clinical experiment was done after it was pointed out by the manufacturers that the earlier preparations of histaminase were sometimes unstable. New material was obtained. Forty-one patients were given 120 units daily, starting just as soon as urticaria appeared and continuing until it disappeared. The treated were compared with forty-one untreated patients with urticaria. Comparisons were difficult to make. The normal as well as the treated individuals lost their urticaria between one and seven to eight days. There was no striking directive tendency noticed when cases were analyzed and grouped according to the time of recovery of the patients, nor were there any startling improvements noticed in any individual patient.

This experience ran counter to that reported in the literature. Alexander[6] collected case reports of over 150 patients with urticaria who were beneficially treated with Torantil. He mentions one report where histaminase failed to benefit twenty-nine patients.

The reports in the literature were again examined. They seemed to us at times varying and vague. The especial recommendation that in severe types of serum sickness 25 units be given from four to six times daily until there is improvement meant nothing, since most patients begin to recover anyway within forty-eight hours.

Since it was difficult for us to detect any difference between our control and treated patients, a fourth and more conclusive clinical experiment was planned. In epidemic meningitis, urticaria is one of the complications of serum therapy in nearly 100 per cent of the patients treated. In brief, here we had a disease which, when treated with serum intravenously, is always followed by serum sickness. It was decided to determine whether Torantil (histaminase) would prevent or modify this serum sickness. It was thought that if we gave Torantil as soon as the patient was given antitoxin, we could determine whether it prevented serum sickness and whether it modified its course.

The meningococcic antitoxin was given intravenously to sixty-five patients, sixty-three of whom received 100,000 or more units. The two exceptions received 60,000 and 70,000 units, respectively. Thirty-six of the patients were treated with histaminase; twenty-nine were not. The drug was given orally daily for ten days, starting either on the day of antitoxin administration if admitted early in the day or the day following if admitted late at night. The dose was at least sixteen

and usually twenty tablets daily in twenty-four patients. Eight patients received from twelve to fifteen tablets daily. The drug was given as long as the serum sickness lasted. Thus, the treatment was both prophylactic and therapeutic. No patients was treated for less than eight days, a total of at least from 128 to 160 tablets (from 640 to 800 units).

Of the thirty-six patients receiving histaminase, thirty-four, or 94 per cent, had serum sickness; of the twenty-nine patients receiving no histaminase, twenty-three, or 79 per cent, had serum sickness. Conversely, two, or 6 per cent, of those treated escaped a serum reaction as contrasted with six, or 21 per cent, of those untreated. There was actually a higher percentage of serum reactions among the patients who received histaminase, although this is not of great statistical significance.

In the patients receiving histaminase, the reactions lasted from one to ten days, the average being 4.6 days; in those in the control group, they lasted from one to twelve days, the average being 4.8. Thus, there was no essential difference in the duration of the serum sickness in the patients in the two series.

COMMENT

One investigator considered results to be good when symptoms disappeared in from one to four days after the onset of treatment but presented no evidence as to the duration of serum sickness in untreated patients. Similarly, in those reports in which histaminase was credited with having prevented serum sickness, no controls were included; that is, no data were given as to the incidence of reactions to be expected with the particular types of sera used. Until such controlled studies are made, it must, perhaps, be admitted that the reactions caused by the various types of horse and goat sera used in the previous reports may be more amenable to histaminase than the reactions following the use of meningococcic antitoxin. This, however, does not seem likely.

CONCLUSION

Histaminase neither prevents nor ameliorates the serum sickness which follows the administration of meningococcus antitoxin (horse).

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RIBOFLAVIN, PANTOTHENIC ACID, AND BIOTIN EXCRETION TESTS IN PATIENTS WITH PARALYTIC POLIOMYELITIS

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Ward and associates[1] have recently reported on the status of thiamine deficiency in paralytic poliomyelitis. They concluded that this deficiency was not the factor which determines "whether infection by poliomyelitis virus shall result in the paralytic or one of the non-paralytic forms of the disease." They also ruled out nicotinic acid deficiency as a factor.

The urinary excretion of riboflavin, pantothenic acid, and biotin was determined in ten patients acutely ill with poliomyelitis within twenty-four hours of hospital admission (Cleveland epidemic of 1941).

Twenty-four-hour specimens of urine were obtained. The amount passed by two individuals was low, only 240 c.c. of urine being obtained in one instance and 259 c.c. in the other. Both of these patients had bulbar poliomyelitis and were on a limited fluid intake. Their second twenty-four-hour specimens were about the same in amount. The total vitamin output was not relatively less, however, than that found in those who passed greater amounts of urine.

The vitamins were assayed by the Snell and Strong method[2] for riboflavin, the Pennington, Snell, and Williams method[3] for pantothenic acid, and the Snell, Eakin, and Williams and the Landy and Dicken methods[4, 5] for biotin. The results of the test are tabulated in Table I.

Table I

Poliomyelitis Patients

Patient	Vol. (c.c.) of 24-hr. urine samples	Riboflavin		Pantothenic acid		Biotin	
		γ per c.c.	γ total	γ per c.c.	γ total	γ per c.c.	γ total
1. W. S.	490	4.13	2,024	6.53	3,200	.031	15.2
2. J. C.	770	2.28	1,756	7.91	6,091	.037	28.5
3. A. M.	1,010	1.48	1,495	3.37	3,404	.009	9.1
4. R. S.	240	3.14	754	11.13	2,671	.045	10.8
5. E. P.	1,640	0.57	935	1.98	3,247	.0079	12.9
6. W. W.	4,644	0.3	1,393	0.42	1,950	.011	51.1
7. R. W.	3,280	0.32	1,050	1.52	4,986	.006	19.7
8. A. N.	474	1.19	564	4.25	2,015	.038	18.0
9. D. S.	1,430	0.95	1,359	2.67	3,818	.015	21.5
10. M. B.	259	4.23	1,096	8.08	2,093	.074	19.2
Totals	14,237.0		12,426.0		33,475.0		206.0
Average	1,423.7	0.87	1,242.6	2.35	3,347.5	.0144	20.6

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The normal content of biotin in the urine is unknown, but in a series of seven patients convalescent from scarlet fever tested simultaneously, the total biotin content was 5.88 γ as compared to 20.6 for the poliomyelitis patients or in the ratio of 1.0 to 3.5 in favor of poliomyelitis. While fairly wide variations may occur in normal subjects, the excretion of riboflavin in the urine may be between 500 and 800 γ[6] and pantothenic acid, from 1,460 to 6,760 γ,[7] with an average of 3,810 γ in nine patients. The values for pantothenic acid were within normal limits. In eight of the ten specimens examined, the riboflavin values were higher than those found in the normal specimens tested by Strong, Feeney, Moore, and Parsons.[6]

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ACUTE SEROUS MENINGITIS IN SCARLET FEVER

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REPORTED cases of central nervous system involvement in the course of scarlet fever are extremely rare. Even more rare are reports of an acute serous meningitis occurring early in the disease. This latter syndrome apparently has been described in only twenty-four patients, all reported from Europe.[3-6]

Within recent months we have seen eleven patients who developed an acute serous meningitis between five and eight days after the onset of scarlet fever. The complication came after the acute symptoms began to decline and was unrelated to other septic foci in the body. The purpose of this paper is to describe this unusual syndrome which heretofore apparently has not been reported in the American or English literature.

CLINICAL MANIFESTATIONS

Between July 1, 1938, and June 30, 1943, there have been 1,503 patients with scarlet fever treated on the contagious disease service of the Gallinger Municipal Hosptial. During this time there have been eleven children who have presented a uniform and striking clinical picture of an acute serous meningitis complicating scarlet fever. The children have been between 3 and 9 years of age, three of them being 7 years of age, and three, 8 years of age (Table I). Six of the patients were boys and five were girls; four were white and seven were Negro children. (This is approximately the proportion of white and Negro patients found in the total admissions to this service.) These patients were seen principally in the spring and fall. Three of them became ill in September, two in October, two in March, and one each in February, April, May, and June. Ten of the patients showed a moderately or severely toxic scarlet fever with a brilliant, characteristic rash and a severe angina. The eleventh child had a typical mild scarlet fever. In five patients there was definite membrane formation on the acutely inflamed tonsils. In one instance this was so suggestive as to cause us to administer diphtheria antitoxin to the patient on admission, although she was found later not to have diphtheria. Scarlet fever streptococcus antitoxin was given to seven of the eleven children on admission or shortly thereafter, and sulfonamides were administered to five of the patients because of either a catarrhal otitis media or a mild acute cervical

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TABLE I

CLINICAL FEATURES OF ELEVEN CASES OF SEROUS MENINGITIS COMPLICATING SCARLET FEVER

CASE	RACE	SEX	AGE (YR.)	ORIGINAL SCARLET FEVER					COMPLICATING MENINGITIS			
				DATE OF ONSET	TYPE	TEMP. (° F.)	SERUM	SULFONAMIDE	DAYS AFTER ONSET OF SCARLET FEVER	TEMP. (° F.)	ADDITIONAL TREATMENT	DURATION OF FEVER (DAYS)
1	W.	F.	7	10/14/40	Toxic	104.4	12,000	Sulfanilamide	7	104.0	Sulfapyridine	5
2	N.	F.	8	2/27/41	Toxic	104.8	18,000	0	8	103.6	0	6
3	N.	F.	4	10/ 2/41	Toxic	103.8	18,000	0	7	105.0	Sulfanilamide	6
4	W.	M.	5	9/27/42	Toxic	104.0	18,000	Sulfanilamide	6	105.0	0	6
5	N.	F.	7	9/26/42	Mod. toxic	103.2	9,000	0	7	104.4	Sulfanilamide	9
6	W.	M.	3	9/29/42	Mod. toxic	104.2	9,000	0	5	104.4	Sulfanilamide	8
7	N.	M.	7	3/ 7/43	Toxic	103.0	9,000	Sulfadiazine	6	103.4	0	5
8	N.	M.	9	3/20/43	Toxic	104.0	0	Sulfathiazole	5	104.2	0	6
9	W.	M.	9	4/14/43	Mod. toxic	103.4	0	0	5	103.0	Sulfathiazole	7
10	N.	F.	8	5/19/43	Mod. toxic	103.2	0	Sulfathiazole	5	102.4	0	8
11	N.	M.	8	6/ 7/43	Mild	102.0	0	0	7	102.0	Sulfanilamide	7

adenitis. In ten of the eleven patients the response to the initial therapy seemed to be good. The temperature dropped to normal, or to very slightly above normal, and there was a lessening of the rash and angina. One child who received only sulfonamide therapy continued to have a fever until the meningitis appeared. In all other patients there was a recurrence of fever between the fifth and eighth days after the onset of the scarlet fever, the temperature rising to levels between 102 and 105° F. and remaining elevated for from five to nine days. With this secondary fever, there usually was vomiting, marked toxemia, and often dehydration. The blood showed leucocyte counts ranging from 11,800 to 32,000 with an increase in immature neutrophiles. Examination immediately after the secondary rise in temperature revealed no adequate explanation for the fever. In no instance was there suppurative otitis media, mastoiditis, sinusitis, or any other septic focus near the meninges, nor was there an exacerbation of the angina or rash in any of the patients.

Within four days after the secondary rise in temperature, all of these patients developed definite signs of meningeal irritation characterized by greater or less resistance to flexion of the neck, usually accompanied by positive Kernig and Brudzinski signs. The tendon reflexes and other signs were variable. In no instance were there cranial nerve or other palsies, nor did any of the patients show lethargy or other evidence of encephalitis.

The cerebrospinal fluid showed consistent abnormalities (Table II). There was a pleocytosis in all instances. This ranged from 32 to 1,100 cells per cubic millimeter, with all except two patients having over 100 cells. The differential count of the spinal fluid showed from 75 to 100 per cent lymphocytes. In nine patients 90 per cent or more of the cells were lymphocytes. In all instances the cerebrospinal fluid sugar was normal, ranging from 43 to 76 mm. per cent. The protein was moderately increased in nine patients, the amount varying from 50 to 100 mg. per cent in the six with quantitative determinations. The spinal fluid was found to be essentially normal within from eight to twenty-eight days after the secondary rise in temperature. There were no organisms on smear or culture of the spinal fluid of nine patients. In the case of one child, the spinal fluid culture on one occasion only contained a large gram-positive coccus that grew in pairs and tetrads. A single specimen from another child contained an organism of the colon group. Both of these organisms presumably were contaminants.

The clinical course of all patients was very similar (Figs. 1, 2, and 3). After two or three days, usually immediately after the spinal tap, the patients' fever began to lessen, and the symptoms to abate. The patients were afebrile and well established in convalescence within five to nine days after the onset of the secondary fever, and within eleven to sixteen days after the onset of the scarlet fever. All have recovered and have remained without sequelae to the present time.

TABLE II

LABORATORY FINDINGS IN ELEVEN CASES OF SEROUS MENINGITIS COMPLICATING SCARLET FEVER

CASE	BLOOD			SPINAL FLUID						
	W.B.C.	P.M.N. (%)	YOUNG P.M.N (%)	TOTAL CELLS	LYMPHO-CYTES (%)	SUGAR MG. (%)	PROTEIN MG. (%)	CHLORIDE MG. (%)	CULTURE	DAYS UNTIL NORMAL
1	12,700	72	25	1,100	75	74	-	610	Contaminated	17
2	32,000	82	30	400	80	Normal*	-	-	Sterile	Not recorded
3	24,400	63	11	640	98	74	-	-	Sterile	26
4	26,650	69	15	200	94	57	100	677	Sterile	7
5	-	-	-	207	95	55	60	693	Sterile	6
6	-	-	-	130	90	71	100	627	Sterile	Not recorded
7	-	-	-	173	90	76	65	-	Sterile	9
8	17,000	75	20	32	100	71	65	644	Sterile	12
9	11,800	86	12	174	97	43	50	660	Contaminated	12
10	15,000	-	-	112	100	65	25	677	Sterile	17
11	31,000	84	34	56	100	70	-	611	Sterile	9

*Qualitative test only.

TABLE III

VIRUS STUDIES OF SPINAL FLUID OF ELEVEN PATIENTS WITH SEROUS MENINGITIS COMPLICATING SCARLET FEVER

CASE	TYPE AND NUMBER OF ANIMALS	WHERE INOCULATED*	AMOUNT (C.C.)	RESULT	COMMENT
1	6 white mice	I.C. I.P.	0.03 0.25	No virus obtained	Blood did not neutralize the virus of lymphocytic choriomeningitis two years after illness
2	5 white mice 1 guinea pig	I.C. I.P.	0.03 3.0	No virus obtained	Blood did not neutralize the virus of lymphocytic choriomeningitis eighteen months after illness
3					No studies made
4	6 white mice	I.C.	0.03	4 died of contaminant infection; 2 negative for virus	
5	6 white mice	I.C. I.P.	0.03 0.25	1 died of contaminant infection; 5 negative for virus	
6	6 white mice	I.C. I.P.	0.03 0.25	No virus obtained	
7	1 monkey	I.C. I.P. S.C. Conj.	1.25 3.0 2.0 0.5	Normal six weeks after inoculation	
8	2 hamsters 2 white rats 2 cotton rats	I.C.	0.8	No virus obtained	
	1 rabbit	I.P. Testicle	2.0 1.0		
9	1 rabbit	Testicle S.C.	1.0 2.0	Died on fourteenth day—cause unknown	
	1 guinea pig	I.P.	3.0	No virus recovered	
10	2 guinea pigs	I.C. I.P.	0.15 4.0	No virus recovered	
	2 hamsters	I.C. I.P.	0.06 2.0	No virus recovered	
11					No studies made

*I.C., intracerebrally; I.P., intraperitoneally; S.C., subcutaneously; Conj., dropped into conjunctival sac.

VIRUS STUDIES

An attempt has been made to isolate a virus from the spinal fluid obtained from nine of these patients. The fluid was refrigerated in ice immediately after it was drawn and was sent by special messenger to the National Institute of Health, Bethesda, Md., where virus studies were done by Dr. Charles Armstrong or Dr. Michael L. Furculow. The results of this work are shown in Table III. The spinal fluid from one patient was injected intracerebrally into white mice, and that from three patients was injected both intracerebrally and intraperitoneally into mice. The fluid from one patient was injected intracerebrally into mice and intraperitoneally into a guinea pig. The fluid from another patient was injected intracerebrally into hamsters, white rats, and cotton rats and intraperitoneally and into the testicle of a rabbit; the fluid from another was injected intracerebrally, intraperitoneally, and subcutaneously and was dropped into the conjunctival sac of a monkey. The fluid from the next patient was injected intratesticularly and subcutaneously into a rabbit and intraperitoneally into a guinea pig. Two guinea pigs and two hamsters received intracerebral and intraperitoneal injections of spinal fluid from the last patient tested. No virus was recovered from any of the patients. The blood from two patients was tested immediately and after eighteen and twenty-four months, respectively, following the illness for neutralizing antibodies against the virus of lymphocytic choriomeningitis. No such antibodies were demonstrated in either patient.

CASE REPORTS

CASE 1.—M. V. W., a white female, 7 years of age, was admitted to the hospital Oct. 18, 1940, with a scarlet fever of four days' duration. The patient had had measles and tonsillitis but no other illnesses. Both parents and three siblings were in good health. The patient presented the picture of a typical rather severe, toxic scarlet fever. There was a small yellowish membrane on the left tonsil. The physical findings were otherwise within normal limits. The child was given general supportive care. In addition, she received an intramuscular injection of 12,000 units of scarlet fever antitoxin and sulfanilamide by mouth. Her temperature dropped sharply from 104.4° F. on admission to 99° F. the following morning (Fig. 1). Her general condition improved, and her temperature remained normal for two days. The sulfanilamide was discontinued, after which the temperature promptly rose, on October 21, to 103.6° F. The following day the temperature was 104° F., and the patient was extremely ill. The lips were dry and cracked, the respirations were increased to 30 per minute, and there was dilatation of the alae nasi. The angina and rash of scarlet fever were less than on admission. The chest was clear to percussion and auscultation. There was a marked nuchal rigidity, and the Kernig and Brudzinski signs were positive.

A lumbar tap was performed. The cerebrospinal fluid was opalescent in appearance. There were 1,100 cells per cubic millimeter, of which approximately 75 per cent were lymphocytes and 25 per cent were polymorphonuclears. The sugar was 74 mg. per cent; chlorides, 610 mg. per cent; protein, 85 mg. per cent; colloidal gold reaction, 0013310000; Kahn, negative. The spinal fluid culture was con-

taminated by a large gram-positive coccus that grew in pairs and tetrads. The blood showed a secondary anemia with 3.4 million erythrocytes and 65 per cent hemoglobin; the leucocytes numbered 12,700 per cubic millimeter, with 72 per cent polymorphonuclear neutrophiles (of which 25 per cent were band forms), 24 per cent lymphocytes, and 4 per cent monocytes. A blood culture showed no growth. The blood Kahn was 3 plus; later it was repeatedly negative.

It was thought at first (erroneously) that the patient might have a streptococcal meningitis that had been modified by the sulfonamide therapy. The blood sulfanilamide level was 3.6 mg. per cent. Sulfanilamide was discontinued and sulfapyridine was given in large doses. On October 23 the cells in the cerebrospinal fluid had dropped to 460 per cubic millimeter, the sugar remained normal, and the culture was sterile. The child's temperature dropped rapidly and returned to normal on October 26. On October 25 the blood sulfapyridine level reached 38.5 mg. per cent. The dosage was reduced after which the level rapidly decreased. The cerebrospinal fluid on October 25 showed 160 cells, a normal sugar, and a sterile culture.

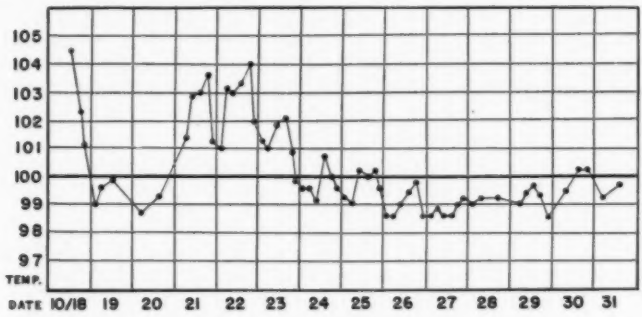

Fig. 1.—The rectal temperature curve of M. V. W. (Case 1), with scarlet fever complicated by acute serous meningitis.

The clinical picture continued to improve until October 29, when the patient developed a generalized morbilliform eruption from the sulfapyridine. The drug was discontinued and the rash faded in two days.

On Nov. 8, 1940, the cerebrospinal fluid contained only 3 cells per cubic millimeter and was in every way normal. The child was discharged in good condition on Nov. 15, 1940. She was last seen on Nov. 17, 1942, when she was in good general condition. She showed no sequelae to her illness.

The spinal fluid withdrawn on Oct. 23, 1940, was chilled immediately and sent to the National Institute of Health. White mice received 0.03 c.c. intracerebrally and 0.25 c.c. intraperitoneally. One week later two mice were sacrificed. No abnormal pathology was found. An emulsion of the organs of these mice was transferred to six additional mice. No illness resulted in the mice before they were discarded on Dec. 20, 1940. Blood withdrawn on Oct. 23, 1940, and Nov. 17, 1942, was tested for neutralizing antibodies against the virus of lymphocytic choriomeningitis. No such antibodies were demonstrated.

CASE 2.—F. H., a Negro female, 8 years of age, was admitted to the hospital March 2, 1941, with a scarlet fever of three days' duration. She had had pertussis and tonsillitis but no other illnesses. Both parents and seven siblings were in good health. The child had a typical, severe scarlet fever. The temperature was 104.8° F.; pulse, 120. Both tonsils were covered with gray, necrotic membrane. There were no other abnormal physical findings.

The child was put to bed and given supportive care. She received 18,000 units of scarlet fever antitoxin and 20,000 units of diphtheria antitoxin intramuscularly. Her temperature dropped to 99.6° on March 3, and remained within the normal range until March 6, her general condition meanwhile showing considerable improvement. Throat cultures for diphtheria bacilli were negative.

On March 6 the child appeared toxic and irritable. Her temperature rose to 103.4° F. without evident cause. Her angina and rash were less severe than on entry. There was slight nuchal rigidity. The following day her neck was much stiffer, and the Kernig sign was positive. A spinal puncture was done. The cerebrospinal fluid contained 400 cells per cubic millimeter, of which 80 per cent were lymphocytes. Spinal fluid sugar was normal. The culture showed no growth. The following morning the cerebrospinal fluid contained 150 cells, mostly lymphocytes, and a normal sugar. The patient's temperature subsided by lysis and was normal on and after March 12. Thereafter her convalescence was uneventful. She was discharged in good condition on March 30, 1941. She was seen Oct. 24, 1942, when she was in good condition. She showed no evidence of sequelae of her illness.

The second specimen of spinal fluid was chilled immediately and sent to the National Institute of Health. Five mice each received 0.03 c.c. spinal fluid intracerebrally. Two mice died of unrelated causes with no evidence of a virus infection, and three remained free from illness until they were discarded April 18, 1941, over five weeks after inoculation. A guinea pig was inoculated with 3 c.c. spinal fluid intraperitoneally. The pig remained free of symptoms.

Serum virus neutralization tests against the virus of lymphocytic choriomeningitis were done on blood withdrawn from the child March 11, 1941, and Oct. 24, 1942. Both sera were negative.

CASE 3.—R. G., a Negro female, 4 years of age, was admitted to the hospital Oct. 4, 1941, with a scarlet fever of two days' duration. She had had no previous illness. Her parents and two siblings were well. She presented a clinical picture of a severe, toxic scarlet fever. The temperature was 103.8° F.; pulse, 110; respirations, 28. She had a severe angina with marked congestion and inflammation of the pharynx and tonsils but no membrane formation. The anterior cervical glands were slightly enlarged and tender. There were no other abnormal physical findings. The child was put to bed and given general supportive care. She improved slowly but on October 7 still showed an acute rash and a severe angina and maintained a temperature of 102.° F. She was given 18,000 units of scarlet fever antitoxin intramuscularly. The next day her temperature dropped to 100° F. but on October 9 rose again and reached 105.4° F. on October 10. On that day she was very toxic and ill. The only significant findings were marked nuchal rigidity and a positive Kernig sign. Sulfathiazole was started by mouth on October 9.

A spinal tap was done on October 10. The cerebrospinal fluid contained 640 cells per cubic millimeter, of which 78 per cent were lymphocytes; the sugar was 74 mg. per cent; Kahn, negative; colloidal gold, 0000000000. The following day the cerebrospinal fluid contained 313 cells per cubic millimeter, with 98 per cent lymphocytes. The culture was sterile. The fluid was otherwise as previously reported. Blood counts showed a secondary anemia with 2.67 million erythrocytes and 50 per cent hemoglobin, 24,400 leucocytes with 63 per cent neutrophiles (of which 11 per cent were bands), 35 per cent lymphocytes, and 2 per cent monocytes. The blood sulfathiazole level was 7.0 mg. per cent. The patient's temperature and pulse gradually subsided after October 10 and was normal on and after October 16. There was an associated improvement in her general physical condition. On October 15 the spinal fluid contained 105 cells per cubic millimeter and on October 20, 28 cells per cubic millimeter of which 95 per cent were lymphocytes. On November 5 there were only 15 lymphocytes per cubic millimeter.

The child was discharged in good condition on Nov. 10, 1941. She was seen last in October, 1942, when she was in very good condition. She had been entirely well since her discharge.

CASE 4.—C. M., a white male, 5 years of age, was admitted to the hospital Sept. 30, 1942, with a scarlet fever of three days' duration. He had had measles when he was 2 years of age; the past history was otherwise noncontributory. Both parents and one sibling, 20 months of age, were in good health.

Examination on admission revealed an acutely ill white male child with typical moderately severe and toxic scarlet fever. The temperature was 104° F. (rectally); pulse, 105. The cervical lymph glands were slightly enlarged and tender. The tonsils were greatly enlarged and cryptic, with some areas of membrane formation. There were no other relevant physical findings.

The patient was given 18,000 units of scarlet fever antitoxin intramuscularly immediately after admission and was started on sulfanilamide. His rash and angina subsided, and his temperature dropped slowly from 104° F. to 100° F. during the next two days (Fig. 2); then the temperature rose again sharply to 103° F.

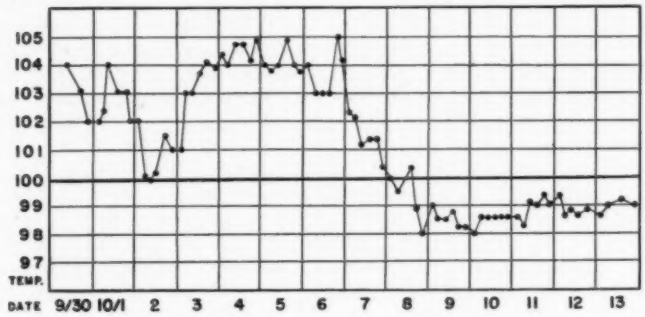

Fig. 2.—The rectal temperature of C. M. (Case 4).

There were no localized physical findings to suggest the cause of the fever. On October 5, eight days after the onset of the scarlet fever and three days after the secondary rise in temperature, the temperature was 105° F., and there was a definite stiffness of the neck and back. Kernig's sign was negative. A spinal puncture was performed. The cerbrospinal fluid was clear. There were 180 white blood cells per cubic millimeter, of which 94 per cent were lymphocytes. The spinal fluid sugar was 57.5 mg. per cent; protein, 100 mg. per cent. Kahn tests on blood and spinal fluid were negative. Colloidal gold curve was 0000000000. The blood showed 3.25 million erythrocytes, 64 per cent hemoglobin, 25,650 leucocytes, with a differential count of 69 per cent polymorphonuclear neutrophiles (of which 15 per cent were band forms), 28 per cent lymphocytes, and 3 per cent monocytes. Free sulfanilamide in the blood measured 13 mg. per cent. Urinalysis was negative.

When the diagnosis of serous meningitis was made, the administration of sulfanilamide was discontinued. During the next three days the temperature fell by lysis to normal. The patient's general condition improved remarkably. On October 12, seven days after the diagnosis of serous meningitis, the cerebrospinal fluid showed no cells and a sugar of 70.0 mg. per cent. The following day the blood leucocyte count was 9,500. Thereafter the patient made an uneventful convalescence. He was discharged October 22 in good condition. He was last seen March 19, 1943, at which time he showed slight undernutrition but no other abnormalities. There were no sequelae of his illness.

On October 6 cerebrospinal fluid was obtained, immediately refrigerated, and sent to the national Institute of Health. Six mice were each inoculated with 0.03 c.c. fluid intracerebrally. The fluid was contaminated and four mice died ten days after of bacterial infections. The remaining mice were sacrificed October 19 and an emulsion of their organs was injected, after filtration, into six additional mice. These mice were free from symptoms until they were discarded on Nov. 23, 1942.

CASE 5.—V. G., a Negro female, 7 years of age, was admitted to the hospital Oct. 1, 1942, with a scarlet fever of five days' duration. She previously had had chicken pox, whooping cough, and measles. Her parents and five siblings were in good health. Examination on admission revealed an acutely ill Negro girl with a typical moderately severe, toxic scarlet fever. The temperature was 103.2° F., pulse, 110. The tonsils were enlarged and injected without membrane formation. There were no other relevant physical findings.

The patient was given 9,000 units of scarlet fever antitoxin. There was a subsequent sharp drop in temperature and pulse with essentially normal readings on the second hospital day. On October 3, the third hospital day, the temperature rose again, however, to 104.4° F. There were no concomitant signs of localized infection. Sulfanilamide was administered to the child orally. The temperature remained elevated, and on October 5 there was slight stiffness of the neck and back. The Kernig sign was negative. A spinal puncture was performed. The cerebrospinal fluid was clear but contained 207 cells, of which 95 per cent were lymphocytes. The sugar was 55.4 mg. per cent; protein, 60 mg. per cent; colloidal gold curve, 0000000000; Kahn test, negative.

Following the spinal puncture, the temperature gradually fell by lysis. It was within the normal range on and after Oct. 12, 1942. The general condition of the patient improved with the fall of temperature. On October 12 a repeat spinal puncture revealed a clear cerebrospinal fluid with no cells and a sugar of 68.4 mg. per cent. The child was discharged to her parents Oct. 25, 1942. She was last seen in December, 1942, when she was in good condition. There were no sequelae of the illness.

Cerebrospinal fluid withdrawn on October 5 and 6 was refrigerated immediately and sent to the National Institute of Health. Six mice were inoculated with 0.03 c.c. intracerebrally and 0.25 c.c. intraperitoneally. One mouse died eight days later of bacterial contamination. The remaining five mice remained free of symptoms and were discarded Nov. 23, 1942.

CASE 6.—J. S., a white male, 3 years of age, was admitted to the hospital Oct. 1, 1942, with a scarlet fever of two days' duration. The past and family histories revealed no relevant illnesses. Examination on admission showed a typical mild scarlet fever. The temperature was 102° F.; pulse, 120. The patient was given supportive treatment, and the next day his temperature rose to 104.2° F. and he became moderately toxic. He was given 9,000 units of scarlet fever antitoxin. This was followed by a prompt fall of temperature to 100° F. There was a concomitant improvement in the child's general condition. On October 4 and 5 the temperature rose again to 104° F. There was slight increase in the size of the cervical lymph glands, and a continuing, but not more severe, tonsillitis. The patient was given sulfanilamide orally without effect. The temperature was maintained without other localized evidences of infection until Oct. 8, 1942, when moderate nuchal rigidity was noted. A lumbar subarachnoid tap was done. The cerebrospinal fluid was clear but showed 130 cells, of which 90 per cent were lymphocytes; the sugar was 70.6 mg. per cent and the protein was 100 mg. per cent. Following the spinal tap the patient's temperature declined steadily and was normal on and after Oct. 12, 1942. A repeat spinal tap October 12 showed a pleocytosis of 20 cells per cubic millimeter.

The protein remained at 100 mg. per cent and the sugar was 68.1 mg. per cent. On October 13 the blood leucocytes numbered 10,100 per cubic millimeter. The patient was discharged in good condition Oct. 25, 1942. He was seen Dec. 5, 1942, at which time he was apparently normal. He showed no sequelae of his illness.

Spinal fluid obtained on October 8 was chilled immediately and sent to the National Institute of Health. Six mice were inoculated with 0.03 c.c. intracerebrally and 0.25 c.c. intraperitoneally. All mice remained free of symptoms and were discarded Nov. 23, 1942.

CASE 7.—D. R., a Negro male, 7 years of age, was admitted to the hospital March 10, 1943, with a scarlet fever of three days' duration. He had had measles, pneumonia, whooping cough, and frequent colds since the age of 18 months. His family history was noncontributory.

At the time of admission he presented a classical picture of a severe, toxic scarlet fever with a marked angina. The tonsils were much enlarged, reddened and edematous, and the upper pole of each was covered by a dirty white membrane. The temperature was 103.0° F.; pulse, 110. The anterior cervical glands were slightly enlarged and tender, and there were pulmonary signs suggesting a bronchopneumonia.

The patient was given 9,000 units of scarlet fever antitoxin intramuscularly and received sulfadiazine by mouth as well as supportive care. His temperature fell to normal on March 12, but the next day rose to 101° F. and climbed steadily to 103.4° F. on March 15. The angina and rash of the scarlet fever were less severe than on admission, and the chest was clear by physical examination and by x-ray. The blood sulfadiazine level was 7.9 mg. per cent. There was a moderate nuchal rigidity. A spinal tap was done. The cerebrospinal fluid was clear with a pleocytosis of 130 cells per cubic millimeter, all lymphocytes. The sugar was 75.8 mg. per cent; protein, 65 mg. per cent. The following day there were 173 cells per cubic millimeter of cerebrospinal fluid. The fluid was otherwise unchanged. Following the spinal tap, the temperature dropped rapidly. He was normal on and after March 17, 1942. There was a concomitant improvement of the general condition. On March 23 the cerebrospinal fluid contained 15 cells per cubic millimeter, and the sugar was 70.8. Cultures throughout were sterile. The patient was discharged in good condition April 5, 1943.

Spinal fluid obtained on March 15 and 16 was refrigerated and sent to the National Institute of Health. The fluid was pooled and inoculated into a monkey as follows: 1.25 c.c. intracerebrally, 3.0 c.c. intraperitoneally, and 2.0 c.c. subcutaneously. Another 0.5 c.c. was dropped into the monkey's eye. No fever or symptoms of illness developed in forty-four days of observation.

CASE 8.—B. W., a Negro male, 9 years of age, was admitted to the hospital March 25, 1943. Five days before admission he became ill with a sore throat, swollen neck, and fever. Three days before entry he was admitted to a neighboring hospital. At that time his temperature was 104.0° F. and he had a severe angina with his throat almost closed by edema, enlarged anterior cervical glands on both sides, and a diffuse, erythematous rash. He was given sulfathiazole by mouth and general supportive care. His temperature dropped to 101.0° F. for two days (Fig. 3), but on March 24 it rose again. A diagnosis of scarlet fever was made and the patient was transferred to the Gallinger Hospital March 25. His temperature on admission was 102.6° F.; he was toxic and dehydrated and critically ill. He showed a severe angina, a moderate cervical adenitis, and an acute bronchitis. There was no nuchal rigidity. He was given supportive care, sulfathiazole, and parenteral fluids. The following day he was improved but still very ill. His temperature rose to 104.3° F. and he developed definite stiffness of the neck. The blood showed 12

Gm. hemoglobin, 3.8 million erythrocytes, and 17,000 leucocytes. There were 75 per cent neutrophiles, with 20 per cent immature forms, 24 per cent lymphocytes, and 1 per cent monocytes. The blood Kahn was 3 plus; later, negative. A spinal tap was done. There were 15 lymphocytes and a normal sugar. The following day his temperature was decreasing. A repeat spinal tap showed 32 cells, all lymphocytes. The child's temperature continued to fall and was normal on and after March 30. He was discharged in good condition April 14, 1943.

Cerebrospinal fluid withdrawn on March 26 and 27 was chilled and sent to the National Institute of Health. The serum was pooled and 0.08 c.c. was inoculated intracerebrally into each of two hamsters, two white rats, and two cotton rats. A rabbit received 2.0 c.c. fluid intraperitoneally and 1.0 c.c. into the left testicle. No ill effects were noted in any of the animals.

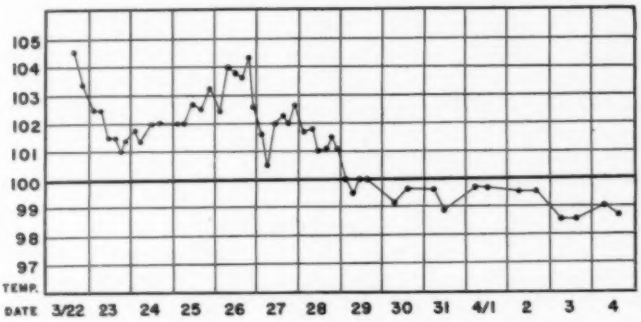

Fig. 3.—The rectal temperature curve of B. W. (Case 8), with an acute serous meningitis complicating scarlet fever.

CASE 9.—R. C., a white male, 9 years of age, was admitted April 16, 1943, with a scarlet fever of two days' duration. He had had measles, whooping cough, and mumps. His parents and three siblings were well. He presented the findings of a typical moderately severe scarlet fever. He had a severe angina with a small amount of white exudate on the left tonsil.

He was given supportive care. His temperature rose from 102° F. on admission to 103.3° F. on the second day and then dropped suddenly to normal. His pulse dropped slowly to 100 per minute. On April 19, three days after admission, his temperature rose again to 101.0° F. He showed a slight catarrhal otitis media, but his rash and angina were subsiding. His temperature ranged from 100 to 102.4° F. for four days, then rose to 103.0° F. He was moderately toxic and dehydrated. His neck was somewhat stiff and the Kernig and Brudzinski signs were positive. A spinal tap returned a cerebrospinal fluid that contained 8 cells; protein, 50 mg. per cent; sugar, 70.5 mg. per cent; a culture showed no growth. His blood contained 11,800 leucocytes, with 86 per cent polymorphonuclears, 12 per cent bands, 1 per cent monocytes, and 12 per cent lymphocytes. He was then given sulfathiazole by mouth for the otitis media, but his symptoms persisted. Two days later, April 25, 1943, a repeat spinal tap showed 174 cells, 97 per cent of which were lymphocytes; sugar, 43 mg. per cent; protein, 50 mg. per cent; and chlorides, 660 mg. per cent. A culture showed a gram-negative bacillus resembling the colon bacillus, considered to be a contaminant.

Following the second spinal tap his temperature dropped to normal and his symptoms subsided gradually. On April 30 the spinal fluid cell count was 98, and on May 7 it had reduced to 18. He was free of symptoms and was discharged.

The spinal fluid obtained on April 25 was chilled and sent to the National Institute of Health. One rabbit received 1.0 c.c. intratesticularly and 2.0 c.c. subcutaneously; and a guinea pig received 3.0 c.c. intraperitoneally. The rabbit died of unknown causes on the fourteenth day. The guinea pig remained free of symptoms and was discarded.

CASE 10.—D. F., a Negro female, 8 years of age, was admitted May 21, 1943, with a moderately severe scarlet fever of two days' duration. She had had measles and pneumonia. Her family history was irrelevant. She was a poorly developed, fairly well-nourished Negro child with a typical, moderately severe scarlet fever. She also had a mild, acute catarrhal otitis media but no other abnormal findings. She was given supportive care but her temperature rose from 100.0° F. on admission to 103.2° F. the following day, and her ears were slightly more inflamed. She was then given sulfathiazole by mouth. Her temperature dropped only slightly and was 102.4° F. on May 25. At that time she showed definite signs of meningeal irritation. A lumbar puncture was performed. The cerebrospinal fluid was clear, contained 112 cells, all lymphocytes; sugar, 64.5 mg. per cent; protein, 25 mg. per cent; and chloride, 67.7 mg. per cent. It was sterile on culture. The blood showed a leucocytosis of 15,000. Following the lumbar puncture the child's temperature dropped sharply, but it maintained a low-grade elevation for eight days, after which it remained normal. The patient had a pleocytosis of 50 cells per cubic millimeter of spinal fluid on June 1, but on June 10 the spinal fluid cell count had fallen to 10. She was discharged in good condition June 12, 1943.

The spinal fluid obtained May 25 was refrigerated and sent to the National Institute of Health. Two guinea pigs were injected with 0.15 c.c. intracerebrally and 4.0 c.c. intraperitoneally. Two hamsters received 0.06 c.c. intracerebrally and 2.0 c.c. intraperitoneally. No virus was recovered from any of the animals.

CASE 11.—E. J., a Negro male, 8 years of age, was admitted June 9, 1943, with a mild scarlet fever of two days' duration. He had had mumps and measles. He showed a typical mild scarlet fever, with slight meningeal irritation. He was given supportive care only. Two days later his temperature was down to 100.0° F. (rectally) but he complained of pain in his neck. A lumbar puncture was performed. The cerebrospinal fluid was entirely normal, with no increase of cells. His temperature was then normal for two days, but on June 14 it rose again to 100.0° F. There was a very slight cervical lymphadenitis, for which sulfanilamide was administered. The temperature continued to rise, however, and on June 17 reached 102.0° F. There was much more marked meningeal irritation. The cerbrospinal fluid was again examined and was found to contain 56 cells per cubic millimeter, all lymphocytes. The sugar was 70.5 mg. per cent; globulin, negative; chlorides, 611 mg. per cent. The blood showed a leucocytosis of 31,000, with 84 per cent neutrophiles (of which 34 per cent were bands) and 16 per cent lymphocytes. Following the spinal tap the patient improved rapidly. His temperature subsided within three days, and on June 25 his spinal fluid cell count was 15. He was discharged in good condition June 30, 1943.

DISCUSSION

These patients present a striking and unique clinical picture and one that has had little discussion. Their conditions apparently are quite different from those of the patients with encephalitis discussed by Top and Gordon,[1] Martin and Champion,[2] and others. They are even more distinct from the meningitis and meningism described by the former

authors. There are few cases of similar illness on record. In 1932 Martin[3] described an acute serous meningitis and an erythema multiforme in an 8-year-old child who had been ill for three days before admission with an indeterminate illness. The cerebrospinal fluid and the temperature curve after admission correspond with those of our patients after the onset of the meningitis. Martin's patient underwent a complete desquamation, typical of that seen in scarlet fever, between the third and tenth hospital days. Presumably, in addition to the erythema multiforme, this was a serous meningitis complicating scarlet fever and was identical with those we are reporting.

In 1936 Olmer and Legre[4] reported a case of a serous meningitis complicating scarlet fever in which meningeal symptoms were apparent from the onset of the disease. The cerebrospinal fluid was normal on the fifth day of illness but showed a pleocytosis and an increase in protein content on the thirteenth day. The clinical picture is not identical with that which we have seen. In 1940 Lassen and Bang[5] reported a group of twenty instances of aseptic complications of the central nervous system in a series of 9,826 cases of scarlet fever. In their group were ten patients whose illness was primarily a meningitis, four in whom there was a meningoencephalitis and six in whom pleocytosis in the spinal fluid was discovered as a result of a spinal puncture done in patients with an unexplained fever. The ten patients with a meningitis closely resemble the ones we have seen and probably are identical with them. They felt that all the conditions, meningoencephalitis, serous meningitis, and pleocytosis spinalis, are variations of the same syndrome. More recently Nielsen[6] has reported six instances of serous meningitis occurring early in scarlet fever.

The nature of the lesion in our patients is unquestionably a serous meningitis. The possibility of the meningeal irritation being due to a meningism is excluded by the marked pleocytosis that occurred in all individuals except two and by the absence of other acute infectious foci at the time of the appearance of the symptoms. There were no septic foci adjacent to the meninges, a fact adequate to warrant the exclusion of an acute aseptic meningitis (classed by Top and Gordon[1] as an acute serous meningitis) due to that cause. The absence of organisms in both smear and culture, the great predominance of lymphocytes in the cerebrospinal fluid, and the normal sugar levels exclude the possibility of an acute pyogenic meningitis. The absence of cranial palsies, of encephalitic symptoms, and of sequelae seems to exclude the diagnosis of acute encephalitis, although Lassen and Bang[5] consider the serous meningitis and meningoencephalitis as different manifestations of the same disorder.

The etiology of the complication is quite uncertain. The clinical features strongly suggest that it is caused by a filtrable virus. To date there are no definite data to confirm this impression.

SUMMARY

We have reported eleven cases of acute serous meningitis occurring within from five to eight days after the onset of scarlet fever. The disease is characterized by fever, meningeal irritation, prostration, and toxemia. The spinal fluid shows a pleocytosis of from 32 to 1,100 cells, almost all lymphocytes, increased protein, and normal sugar. Following lumbar puncture the symptoms subside. No sequelae to the disease have been encountered.

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SERUM DIASTASE IN THE NEWBORN INFANT

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BOTH the origin of blood diastase and its physiologic relationships are still obscure. However, certain empirical observations have been made which are already of proved value in clinical medicine. The changes in the diastatic activity of the blood seen in certain disorders of the pancreas,[1] of the parotid gland,[2] and of the liver[3] have been of particular importance.

In so far as we know, there have been no reports on the diastatic activity of the blood during the neonatal period. We have recently made such observations and believe them to contribute to the general knowledge of this enzyme sufficiently to be worthy of a brief report.

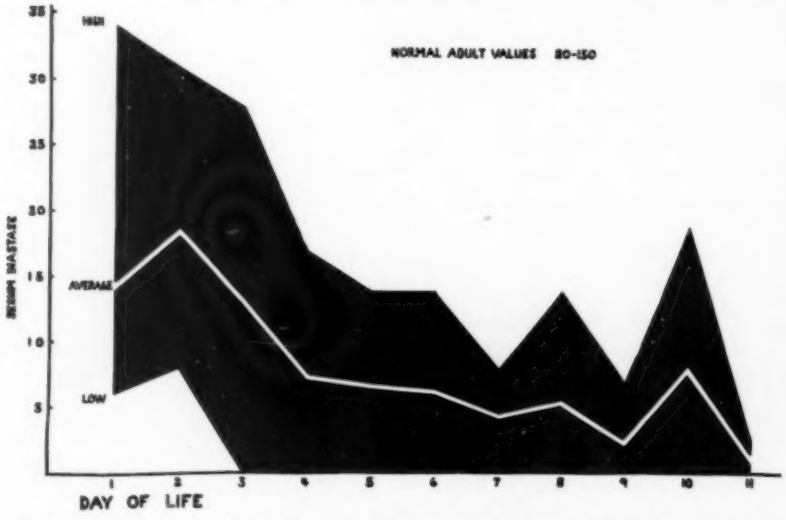

Fig. 1.—Seventy-five diastase determinations on twenty-seven infants during the neonatal period.

Material.—Full-term newborn infants were selected at random from the newborn nursery of the St. Louis City Hospital. Venous blood was obtained from the femoral vein. The infants were followed only until the time of discharge from the hospital. Most of the infants had at least two observations during the neonatal period. Many, however, had three or more so that some idea could be obtained as to the individual as well as the general trend.

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Methods.—The diastatic activity of the serum was determined by the amyloclastic method of Somogyi.[4] In this method the time is measured which is required for a certain amount of serum to affect a starch solution so as to reach an end point determined by means of an iodine solution. Although the degree of accuracy is appreciably decreased if the required time is longer than sixty minutes, the most important fact—that the diastase is very low—can be established (below 30 with the usual starch solutions).

Results.—Seventy-five determinations were performed on twenty-seven infants varying in age from 5 to 252 hours. The highest values were obtained during the first three days of life. The highest individual values obtained during these three days were 34, 31, and 28 for the first, second, and third days, respectively. During the remainder of the period values of below 15 were obtained with but two exceptions. The somewhat higher values obtained in the first three days of life may possibly represent a persistence of enzyme supplied by the mother. These values are strikingly low when compared with the average values of from 80 to 150 obtained in adults. The values obtained were in no way correlated with the sex, birth weight, or icterus index of the infant.

Summary.—

1. The blood during the neonatal period has very little diastatic activity.

2. The highest values obtained during the neonatal period were in the first three days of life. This may possibly represent a persistence of enzyme supplied by the mother.

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PARALYTIC RABIES

Review of the Literature and Report of a Case

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CLASSIC rabies has been known to the medical profession since the time of Aristotle. That the disease might exist in a predominantly paralytic form, however, must have been suspected as early as 1684, when Howmann[1] reported the case of an individual who became paralyzed in the right arm six weeks after being bitten by a rabid fox. After an unspecified number of days he developed typical rabies symptoms and died.

In 1753 Hoin[2] described four cases of "tranquil or paralytic" rabies occurring in a group of seventeen individuals who had been bitten by some rabid wolves.

Gamalia,[3] in 1887, collected and published twenty cases of rabies in which paralysis was the outstanding feature. Four of the patients had received antirabies treatment. All of his patients sooner or later manifested from a few to several "characteristic" symptoms of rabies; that is, difficulty in swallowing, pharyngeal spasms, hydrophobia, aerophobia, mental excitement, erections and ejaculations, excessive salivation, and spitting.

In 1888 Laufenauer[4] reported having seen, over a two-year period, ten patients afflicted with the paralytic form of rabies.

Bamberger,[5] in 1896, reported a case of paralytic rabies in which the patient developed suddenly, while at work, a paresis of the right arm and leg. Subsequently the left leg became involved, though to a lesser degree. There was no disturbance of sensation. Hydrophobic symptoms ultimately appeared, and the patient died on the seventh day after onset. No history of a bite or contact with a rabid animal could be obtained.

In 1906 Remlinger[6] called attention to the rabies virus as being one of the pathogenic agents capable of causing acute ascending paralysis and observed that rabies could occur as a predominantly paralytic disease "in which the paralysis may begin in the lower extremities, rise to the bladder and rectum, spread to the upper limbs, and then to the bulbar nerves." He pointed out that "hydrophobia (may be) reduced to a few pharyngeal spasms occurring shortly before death during the drinking of liquids . . . that an equal degree of difficulty in swallowing may occur as a terminal event in cases of ascending paralysis due to agents other than the rabies virus."

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Van Gehuchten,[7] in 1907, reported a case of paralytic rabies in a 47-year-old man who had been bitten on the chin by a dog thirty-six days prior to the onset of symptoms. The outstanding feature of the disease was a flaccid paralysis which began in the left arm and spread to involve the right arm, trunk, and lower extremities. There were no disturbances of sensation in any part of the body, and during the entire course of the illness (which lasted for fifteen days) no classic rabies symptoms appeared. Van Gehuchten's clinical diagnosis was acute anterior poliomyelitis. However, in the post-mortem studies the anterior horn cells of the spinal cord were found unharmed, and rabbits inoculated with fragments of the brain and spinal cord of the patient died with symptoms typical of rabies.

Babes,[8] in his "Traité de la Rage" (1912), gives the case history of a patient who had been bitten on the right thigh by a dog and became ill from eight to ten months later with "an almost pure ascending paralysis." The entire course of the disease transpired "without hydrophobia and without attacks of fury." Death occurred on the twelfth day after the onset of symptoms, and necropsy revealed "classic rabies nodules" in the bulb, spinal cord, and spinal ganglia. One of the rabbits inoculated with emulsified spinal cord tissue taken from the patient died with symptoms typical of rabies. Babes also gives brief case histories of two other individuals with paralytic rabies, but classic rabies symptoms appeared in these patients four and nine days, respectively, after the onset of paralytic phenomena.

Marie and Chatelin,[9] in 1919, reported a case of paralytic rabies in an 11-year-old child who lived for eighteen days after the onset of symptoms. While a certain degree of mental disturbance accompanied the paralysis (which appeared early), no difficulty in swallowing was noted until the fifteenth day after onset, and he did not refuse fluids until shortly before his death. Post-mortem studies revealed what appeared to be Negri bodies in the spinal cord and brain, especially in the cornu Ammonis. Rabbit inoculation experiments were positive for rabies in two successive passages.

In 1924 Uribe[10] reported the case of a 7-year-old child afflicted with a paralytic disease four weeks after being bitten in the right leg by a mad cat. The disease was ushered in by fever and pain in the left buttock (side opposite the bite). Weakness of the legs was noted on the second day after onset. By the fifth day the lower limbs were rendered completely useless by a flaccid paralysis, which thereafter rapidly ascended, involving the musculature of the trunk and upper limbs. Death occurred on the tenth day. During the last few days of life dysphagia was present, but no pharyngeal spasms or hydrophobia developed. Uribe believed the disease represented an example of paralytic rabies because of the "bite of the mad cat, the coexistence of an epidemic of rabies in the country, and the presence of normal spinal fluid." One

of the features of the illness, "abolition of sensitivity of the skin," was additional evidence helping to rule out poliomyelitis. (Due to the lack of a post-mortem examination, however, this case can only be suspected of being an example of paralytic rabies.)

In 1929 Knutti[11] reported a case of acute ascending paralysis occurring in a 23-year-old student nurse at Vanderbilt University Hospital. Her spinal fluid was found to contain 75 cells per cubic millimeter with an increase in globulin content, and she was given convalescent poliomyelitis serum. However, there developed disturbances of sensation, notably anesthesia of the skin of the left leg, hypesthesia in the right leg, and loss of position sense in the left leg. Transient pain occurred in the right lower quadrant of the abdomen. She died on the ninth day after the onset of symptoms without ever having experienced any difficulty in swallowing, pharyngeal spasms, or hydrophobia. The final clinical diagnosis was "transverse myelitis, ascending." Necropsy, however, revealed that the patient had died of rabies, for Negri bodies were found not only in her spinal cord, but also in the brains of rabbits inoculated with an emulsion of the cord.

In 1936 Roy[12] reported a case of rabies simulating acute transverse myelitis. The disease was ushered in by fever and pain over the upper part of the body. On the third day after onset, however, the child was unable to move his legs; and on the fourth day he was found to have, in addition to paralysis of the lower extremities, complete anesthesia of the skin up to the level of the umbilicus. Urinary retention necessitated repeated catheterizations. It was not until the sixth day, when hydrophobic symptoms appeared, that the rabic nature of the disease became apparent. The child died several hours after spasms and hydrophobia set in. There was no mention of a post-mortem examination. On inquiry the parents recalled that the boy had received a dog bite (site not stated) eight months previously. He had not undergone antirabies treatment. It was subsequently learned that another child bitten by the same dog had died two months previously and had also had paralysis of the limbs.

Corria,[13] in 1938, reported the case of a 10-year-old boy who became ill with pain in the right lower quadrant of the abdomen, nausea, and vomiting. Appendicitis was suspected at first, but after the third day a flaccid paraplegia with incontinence of urine and feces led the attending physician to make a diagnosis of poliomyelitis. High fever and delirium appeared at this time and persisted. Fluids were taken well throughout, and at no time did the patient experience any pharyngeal spasms, hydrophobia, or aerophobia. Respirations became progressively weaker, and the child died on the twelfth day after the onset of symptoms. Rabies was never suspected; there was no history of an animal bite, and no antirabies treatment had been administered. Post-mortem

inoculation studies indicated that death was due to rabies, for Negri bodies were found in the brains of experimental animals.

No discussion of paralytic rabies would be complete without reference to the Trinidad disease.[14-17] In 1931 Hurst and Pawan[14] reported seventeen cases of acute ascending myelitis occurring in native children on the Island of Trinidad. The local practitioners at first thought that the disease was poliomyelitis, and this seemed especially likely since many of the patients in the earlier cases manifested no sensory changes. During the ten-year period 1929-1939,[17] a total of seventy-three cases were recorded, and it was discovered that the disease was due to the rabies virus which was transmitted by the bite of infected vampire bats. (The virus was isolated from the salivary glands of these vectors.[16] After an incubation period varying from three weeks to eleven months, the illness was ushered in acutely by fever and headache and by numbness, "pins-and-needles" sensation, or pain about the site bitten. Weakness of the legs was occasionally the first sign but more often commenced a few days after the onset of the above symptoms. The paresis more or less rapidly developed into complete paralysis and progressed upward, involving the musculature of the trunk and frequently the upper extremities before death ensued. Sensory changes were of variable occurrence. In some of the patients there was loss of sensation to touch, pinprick, and heat and cold from the feet up to the level of the umbilicus or lower ribs. In a few patients "excitement" was present. Dysphagia was often absent or appeared only as a terminal phenomenon. But classical symptoms of rabies were most often entirely absent, and it was only through animal inoculation studies* that the correct diagnosis was evolved. It was suggested that the rabies virus undergoes modification in bats which renders it able to produce only the paralytic form of the disease.

Recently at Vanderbilt University Hospital the following case was seen:

CASE REPORT

T. N. B., a 4½-year-old white boy, was admitted to Vanderbilt University Hospital Nov. 21, 1942. On November 10 he had developed a "head cold" associated with high fever, headache, right-sided abdominal pain, and mild photophobia. On the following day it was discovered that he had lost the use of his legs. A local physician saw him at this time and made a diagnosis of poliomyelitis. The high fever and paralysis persisted. On the eighth day after onset (at which time the temperature was found to be 104° F.) talk became irrational, and the child picked continually at various parts of his body. At night he would frequently cry out in his sleep and would often "wake up scared." He continued to take food and fluids satisfactorily, however, with no difficulty in swallowing. Bowel and urinary

*In a report of the histologic findings in four of their patients, Hurst and Pawan[15] stated that Negri bodies were not seen because sections from the cornu Ammonis were not available for study. However, emulsions of the brain tissue were inoculated intracerebrally into monkeys and rabbits and resulted in the development of rabies symptoms in these animals and Negri bodies were found in the brains of many. Moreover, Negri bodies were found in the tissues of the central nervous system of cattle which had died of the disease as a result of bat bites.

functions were unimpaired. On the eleventh day after onset he was referred to Vanderbilt University Hospital because his local physician believed that he was developing paralysis of the muscles of respiration.

The patient's past history and the family history were noncontributory. He had received no immunizations.

On admission to the hospital his temperature was 101.4° F. rectally. He was quite lethargic, frequently mumbled unintelligibly, and picked at his skin continually. The respirations were chiefly diaphragmatic, the intercostal muscles being used very little. However, breathing was not labored, and there was no dilatation of the alae nasi and no use of the accessory muscles of respiration. There was no cyanosis, but the skin was sallow. The face appeared slightly swollen, and the lips were red. Numerous linear excoriations were present over the trunk, apparently the result of picking and scratching. The eyes manifested no strabismus or nystagmus; the pupils were equal and reacted readily to light. No papilledema was seen on ophthalmoscopic examination. The neck was moderately stiff on forward flexion. The lungs were clear to percussion and auscultation, and the heart was not enlarged. An apical systolic murmur was present, and there was a fairly marked tachycardia (128/min.). Findings in the abdomen were negative. There was a complete flaccid paralysis of the lower extremities, but there was apparently fairly good power in the upper extremities, which were continually moved about as he picked and scratched at himself. Because of his irrational semicomatose condition, sensation could not be adequately tested, but the arms were withdrawn from the site of a pinprick while the legs (which were completely paralyzed) were not. The knee jerks and ankle jerks were absent; the tendon reflexes of the upper extremities were present and equal but hypoactive. The abdominal and cremasteric reflexes could not be elicited. Kernig's sign and Brudzinski's sign were positive. Babinski's sign was not present.

A lumbar puncture was done immediately after admission, and clear spinal fluid was obtained under no increase in pressure. The cell count was 10 per cubic millimeter (mononuclears), the Pandy test was slightly positive, and the sugar content was normal. No growth resulted from culture of the spinal fluid.

The red blood count was 4,300,000 per cubic millimeter with 13 Gm. of hemoglobin per 100 c.c. The white cell count revealed a moderate leucocytosis (20,450 cells per cubic millimeter) with a normal differential count. The Kahn test was negative. A urine specimen was not obtained due to the patient's early death after admission.

The child was given glucose in normal saline intravenously shortly after admission. He improved somewhat following this, became more alert, and began taking fluids by mouth. No spasm or pain was produced by swallowing or by the sight of liquids. He continued to take fruit juices well during the remainder of the night, but on the following morning respirations were becoming weaker, he began to vomit coffee ground material, and expired approximately ten hours after admission. A tentative diagnosis of paralytic rabies was made based on experience with a similar case seen in Vanderbilt University Hospital (Knutti's case described earlier).

A post-mortem examination was performed twenty-four hours after death by Dr. Addison Scoville. The gross examination of the brain revealed congestion of the vessels over the surface; questionable cloudiness of the arachnoid was present. There was a small pressure cone involving the tonsils of the cerebellum. Coronal sections showed some congestion of the vessels in the brain substance. The ventricular system was not dilated or displaced. The spinal cord appeared normal except for slight congestion of the vessels.

Microscopic examination of sections of the cerebral cortex (Fig. 1), cornu Ammonis, and the internal capsule revealed in the neurons bright pink, round or oval, intracytoplasmic inclusions (Negri bodies). Some of the neurons contained two and three Negri bodies. Perivascular round cell infiltration, congestion, and glial

proliferation were also seen in these sections. Many of the neurons showed neuronophagia. In the pars nervosa of the pituitary were small collections of round cells. There was marked round cell infiltration about a few blood vessels of the pars nervosa. In sections of the spinal cord (Fig. 2) the ganglion cells of the gray matter showed degeneration and necrosis in addition to focal increases in microglial

Fig. 1.—Cerebral cortex. Middle neuron shows one Negri body below nucleus. Extreme right neuron shows three poorly defined (out of focus) Negri bodies around nucleus. Carbol aniline fuchsin ×1000.

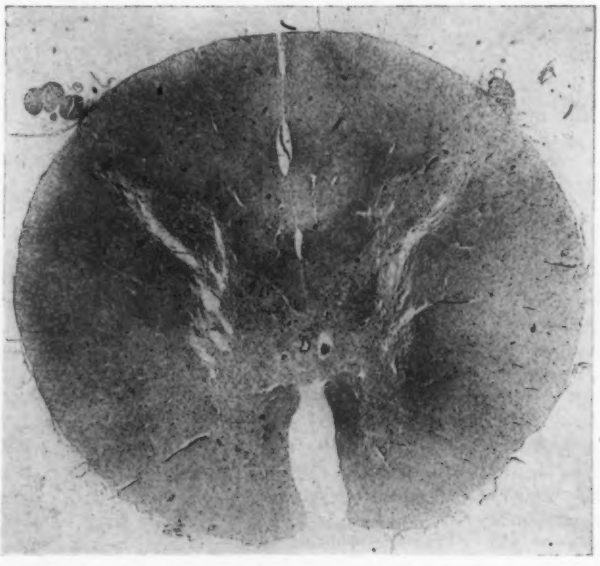

Fig. 2.—Thoracic cord showing distribution of inflammatory reaction. Hematoxylin and eosin ×11.

cells, perivascular round cell infiltration, congestion, and small hemorrhages. These changes were more marked in the posterior horns than in the anterior horns, and the same process was found in the ganglion cells of the dorsal nerve roots. The white matter of the spinal cord showed considerable microglial proliferation in focal areas, small hemorrhages, congestion, and perivascular round cell infiltration.

Sections of the brain stained with carbol aniline fuchsin and methylene blue showed the Negri bodies very distinctly, and in some of these the internal structure could be made out.

The remaining significant necropsy findings were confined to the adrenal glands and the ganglion cells of the plexuses of Meissner and Auerbach of the gastrointestinal tract. There was a large area in the adrenal medulla in which medullary cells were necrotic. A large number of lymphocytes, plasma cells, and mononuclears were present in this area. No Negri bodies were seen. In sections of the pylorus,

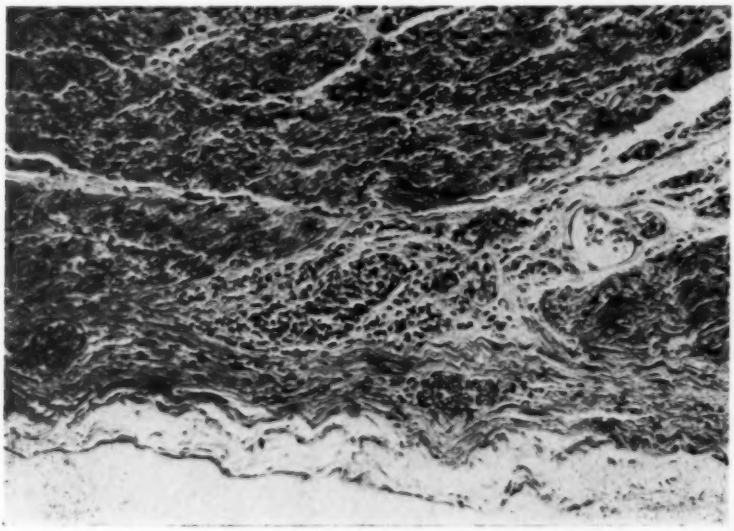

Fig. 3.—Plexus of Auerbach showing necrosis and cellular infiltration. Hematoxylin and eosin ×120.

small intestine (Fig. 3), colon, and appendix there was degeneration of the ganglion cells and an infiltration with lymphocytes and mononuclears in and about them. Although Negri bodies were not found in these sections, it was thought that the changes present were due to rabies. Examination of the lungs showed aspirated material in the bronchi and an early and minimal bronchopneumonia. A post-mortem blood culture was negative.

Fresh brain was inoculated intracerebrally in one rabbit and on the scarified cornea and skin of another. The animal inoculated intracerebrally died shortly after the procedure. The other animal developed paralysis and died. Smears of the brain showed Negri bodies.

After the diagnosis of rabies was established, the public health officer in the patient's home county was written in an effort to obtain a more complete history, including history of dog bite. He replied that the child had been bitten on the nose by a small dog during the latter part of July, 1942; that is, about three and one-half months before the onset of symptoms. "The only sign of where the dog had

bitten him was a little blue knot on the nose between the eyes.'' Shortly after biting the child, the dog was observed to be continually digging in the ground and eating dirt. Within the following week he was killed by his owner, who believed that he had been poisoned. The health officer's letter continued: ''The local doctors who saw the case say they never saw a rabies patient act like this one. . . . We have been able to get very little history of an excitement stage and no history of hydrophobia or difficulty in swallowing.''

DISCUSSION

The ability of the rabies virus to produce a paralytic disease without coexisting classic rabies symptoms is exemplified by the preceding case report and by others found in the literature. In these patients in whom a flaccid paralysis develops many months after a very minor (and perhaps forgotten) animal bite, such diagnoses as ''poliomyelitis,'' ''transverse myelitis,'' and ''Landry's syndrome'' are apt to be proposed unless it is remembered that such an entity as paralytic rabies does exist. Remlinger emphasized the importance of seeking a history of dog bite in all cases of the ''syndrome of Landry.'' Van Gehuchten suggested that many cases previously dismissed as ''ascending paralysis of Landry'' were in reality probably examples of paralytic rabies. If hydrophobic symptoms set in before death (examples, Roy's patient, Gamalia's patients), the rabic nature of the process will be apparent. But if, as in the cases of van Gehuchten, Babes, Uribe, Knutti, Corria, and the case herein reported (T. N. B.), classic rabies symptoms fail to appear, necropsy is necessary to establish the diagnosis.

Relationship Between the Severity of the Bite and the Development of the Paralytic Form of Rabies.—In his important contribution in 1887 focusing attention on the existence of a paralytic type of rabies, Gamalia suggested that the disease was more likely to assume a paralytic form after inoculation with large quantities of virus—such as result from the severe, deep bites of rabid wolves. Marie and Chatelin, on the other hand, called attention to the insignificance of the bite in their patient, the dog having inflicted on the upper lip of the child ''only a slight wound . . . which healed rapidly.'' In the two cases seen at Vanderbilt University Hospital (Knutti's patient and T. N. B.) the bites were of such minor nature as to have been temporarily forgotten.* No history of a bite was ever obtained in Corria's case. The patients of van Gehuchten, Babes, and Uribe had apparently sustained only minor bite wounds; at least the authors did not emphasize the bites as being severe, deep, or multiple.

It appears, therefore, that truly paralytic rabies (unaccompanied by classic symptoms) is more likely to develop after a minor and insignificant-appearing bite. None of Gamalia's patients whose bites were said to have been severe were completely lacking in typical symptoms of rabies.

*Since the publication of Knutti's case report, it has been learned that his patient was bitten by a squirrel. The site of the bite and incubation period were not learned.

Incubation Period and Age of Patients in Paralytic Rabies.—No particular relationship could be drawn between the length of the incubation period and the development of the paralytic form of rabies. The interval between the time of the bite and the time of onset of symptoms varied from four weeks (Uribe's case) up to eight to ten months (Babes' case). The disease seemed capable of appearing in the paralytic form in all age groups. For example, T. N. B. was only 4½ years old, while one of Gamalia's patients was 71 years old.

Relationship Between the Bite Site and the Site of Onset of Paralysis.—Of nineteen patients whose paralysis set in before the appearance of classic rabies symptoms, if indeed the latter appeared at all, twelve (65 per cent) became paralyzed first in the limb which had been bitten. In the remaining seven cases (37 per cent) the paralysis began in a site other than that bitten.

Duration of the Disease When It Appears in the Paralytic Form.—It can probably be stated that when the disease is characterized chiefly by paralysis, with few if any typical rabies symptoms coexisting, it runs a much less fulminating course than does the usual form of rabies. Gamalia seemed quite impressed by the fact that, in his twenty cases of paralytic rabies, the average duration of life after the onset of symptoms was seven and one-half days, "while ordinary rabies has an average duration of only three days." Of the six cases of paralytic rabies cited above in which classic rabies symptoms failed to appear, the average duration of life after the onset of symptoms was nearly twelve days.

Sensory Disturbances.—Sensory disturbances developed to a greater or lesser extent in five of the six patients in whom classic rabies symptoms failed to appear. Babes' patient was disturbed by hyperesthesia of the right leg. Uribe's patient suffered "an abolition of the sensitivity of the skin." In Knutti's patient dull pain in the right lower quadrant of the abdomen was present for a short period of time, and there subsequently developed almost complete anesthesia of the skin of the left leg with diminished sensation in the right leg. There also occurred loss of position sense in the left leg. The onset of the disease in Corria's patient was manifested by pain in the right lower quadrant of the abdomen. T. N. B. also suffered from right-sided abdominal pain at the onset of his illness, and he apparently experienced a severe itching sensation or other paresthesias, for during the three days prior to admission to the hospital he had persistently picked and scratched at his skin. Only van Gehuchten's patient was supposed to have had no disturbances in sensation, but he did experience some pains and tingling in the left arm at the time of onset of paralysis in this limb. In Roy's patient, who ultimately developed hydrophobic symptoms, anesthesia of the skin of the lower extremities and trunk up to the level of the umbilicus appeared early in the disease. It is of interest that the presence of sensory changes in many of the later cases in the Trinidad outbreak of paralytic rabies

led the local practitioners on this island to realize that they were not dealing with poliomyelitis, which had at first been suspected.

Fever.—In the absence of any demonstrable complicating infection, the persistence of fever, or even the first appearance of fever, days after the onset of flaccid paralysis should suggest that the process is not poliomyelitis, in which disease the temperature has usually dropped to normal within the first three to five days after onset. Van Gehuchten's patient, who lived for fifteen days after the onset of symptoms, had a temperature of 38 to 39.4° C. "during his last few days." Babes did not give any temperature readings in his case. Marie and Chatelin's patient, who lived for eighteen days, had a temperature of over 39° C. during the last three days of life. Uribe's patient had a temperature of 38 to 39° C. daily during the ten days of his illness. Corria's patient developed a high fever (temperature, 40° C.) on the fourth day of his illness and continued to have a temperature of 39° C. daily until his death on the twelfth day. The patient herein reported, T. N. B., ran a febrile course throughout the twelve days of his illness, his temperature being 104° F. on the eighth day after onset. It was 101.4° F. at the time of admission to Vanderbilt University Hospital. Knutti's patient had only a low-grade fever, but there was an elevation in temperature to 102° F. two days before death.

Paralytic Rabies and Neuroparalytic Accidents Due to Antirabies Treatment.—Paralysis, especially paraplegia and acute ascending paralysis, is a well-known complication of antirabies treatment. Of the cases of paralytic rabies cited above, none, with the exception of four of Gamalia's twenty patients, had received antirabies treatment after being bitten. In regard to patients receiving preventive inoculations, there naturally arises the question of whether the clinical pictures present represent neuroparalytic accidents due to the prophylactic inoculations or whether they are actually direct manifestations of rabies infection. Van Rooyen and Rhodes[18] cite the criteria enumerated below for differentiating the two entities.

Neuroparalytic accidents due to antirabies treatment are characterized by onset toward the end, or shortly after the completion, of the course of antirabies treatment; absence of hydrophobia or excitement; a high recovery incidence except in the Landry type in which the mortality rate may reach 30 per cent; in fatal cases, absence of lesions characteristic of rabies, notably Negri bodies; absence of street or fixed rabies virus in the brain of the patient.

Paralytic rabies, on the other hand, is characterized by usual incubation period of rabies; paralysis ultimately accompanied by some hydrophobic manifestations;* uniformly fatal termination; histologic picture

*This is not a safe criterion, however, since hydrophobic symptoms may fail to appear, as in the cases of van Gehuchten, Uribe, Knutti, Corria, one of Babes' patients, and the patient in the case herein reported (T. N. B.).

of rabies, including Negri bodies; presence of rabies virus in the brain of the patient.

Since Gamalia's four patients who had received antirabies treatment ultimately developed hydrophobic symptoms, they may properly be included as examples of paralytic rabies according to the above criteria.

Koch,[19] Higier,[20] Lubinski,[21] Fedoroff,[22] Gutmann,[23] and van Wulfften Palthe[24] all reported cases of ascending paralysis suspected of being due to the rabies virus. However, their patients had all received antirabies inoculations beginning within a few days after being bitten. The incubation periods were quite short, between thirteen and twenty-six days, and therefore well within the period when neuroparalytic accidents due to antirabies treatment might be expected to appear. None developed hydrophobic symptoms, and at necropsy Negri bodies were not found in the brains or spinal cords of any of the victims. However, animal inoculation studies resulted in the finding of Negri bodies in the animals injected with brain tissue from the majority of these patients, thus indicating that they had been infected with rabies virus.

Van Wulfften Palthe, in discussing his patient, suggested that the clinical picture produced might conceivably have been modified by the antirabies inoculations; that the symptoms present might represent a combination of postvaccinal paralysis plus actual rabies infection with street virus. It is of interest that the incubation periods in the patients in the cases reported in the preceding paragraph varied between thirteen and twenty-six days, while the incubation periods in those patients with paralytic rabies not receiving prophylactic inoculations were most often stated in terms of months.

Pathology.—The pathologic changes in the spinal cord of the patient herein reported (T. N. B.) consisted of degeneration and necrosis of the ganglion cells in both the anterior and posterior horns of the gray matter. These changes were more severe in the posterior horns. In addition, there were focal increases in microglial cells, perivascular round cell infiltration, congestion, and small hemorrhages in both the gray and white matter of the cord. The ganglion cells of the dorsal nerve roots were similarly involved. Negri bodies were not seen in the sections of the spinal cord examined but were found in abundance in the cerebral cortex, especially in the cornu Ammonis. One of the two rabbits inoculated with an emulsion of the brain died of paralytic rabies, and Negri bodies were found in the central nervous system of this animal.

In Knutti's patient an acute destructive rabic myelitis constituted the anatomic basis of a disease characterized clinically by ascending paralysis and disturbances of sensation. Both the anterior and posterior horns of the gray matter showed extensive necrosis and infiltration of large mononuclear phagocytic cells and lymphocytes. Nearly all the motor ganglion cells of the anterior horns had disappeared com-

pletely; in those remaining, all stages of degeneration were present, and many contained Negri bodies. The ganglion cells of the posterior horns also showed degeneration in all stages. The white matter of the spinal cord likewise showed extensive diffuse destruction with few intact myelinated fibers remaining. There was a diffuse infiltration of large mononuclear leucocytes, most of which contained phagocytosed material. The smaller blood vessels showed marked perivascular rings of lymphocytes. The nerves arising from the dorsal portion of the spinal cord showed lesions varying from slight focal necrosis to extensive destructive changes. The ventral nerves showed only minor changes compared to those arising dorsally. The rabic nature of this patient's illness was established by the finding of Negri bodies in the central nervous system as well as by animal inoculation. Rabbits injected with spinal cord substance from the patient developed a paralytic disease and died; Negri bodies were found at necropsy.

Van Gehuchten was struck by the lack of correspondence between his patient's symptoms and the histologic lesions of the spinal cord. A flaccid paralysis was the outstanding clinical feature, with little or no disturbance in sensation. But at necropsy the motor cells of the anterior horns appeared normal, while there were "profound cellular lesions" in the spinal ganglia. The rabic nature of the patient's illness was proved by animal inoculation. Of three rabbits injected intracerebrally with emulsified brain tissue from the patient, two died with symptoms typical of rabies.

In the patient of Marie and Chatelin the pathologic changes were most marked in the spinal cord and posterior root ganglia. There was intense inflammatory infiltration (both perivascular and parenchymatous) of all the gray matter of the cord with the posterior horns being affected to about the same extent as the anterior horns. The infiltration assumed the form of "rabies nodules of Babes" with intense neuronophagia, hypertrophy of the peripheral intracellular neurofibrils, and disappearance of nuclei. In the protoplasm of certain cells, which were left relatively intact, there were forms resembling Negri bodies. The root ganglia showed intense neuronophagia of the ganglion cells with proliferation of the pericellular capsule. In the cerebral cortex, and more specifically the cornu Ammonis, there were questionable Negri bodies. Rabbit inoculations, in two successive passages, were positive for rabies.

In Corria's case examination of the spinal cord showed "meningeal and central congestion. . . . There was no investigation for the presence of Negri bodies, for there did not exist the least suspicion of rabies." However, post-mortem inoculation studies ultimately resulted in the finding of Negri bodies in experimental animals.

Gamalia did not report the pathology in his cases, and Uribe and Roy apparently did not obtain necropsies in their patients.

Hurst and Pawan's description[15] of the pathologic changes in one of their typical Trinidad cases indicated a fairly close correspondence between the histologic lesions and the clinical symptoms. The spinal cord bore the brunt of the infection and exhibited widespread nerve cell destruction with considerable microglial proliferation. In both gray and white matter there was a marked perivascular infiltration with single or double layers of lymphocytes and often a few polymorphonuclears. At many levels of the cord the microglial proliferation was intense over the whole gray matter and in places in the adjacent white matter. Many of the nerve cells were markedly swollen with complete chromatolysis in the central parts of the cells. A few neurons were necrotic and surrounded by masses of neuronophages. At some levels of the cord practically every nerve cell had succumbed. There was no difficulty in distinguishing the lesions from those of poliomyelitis, for the posterior as well as the anterior horns were affected and to an approximately equal extent. Above the brain stem histologic changes were slight.

SUMMARY AND CONCLUSIONS

1. The virus of rabies may produce a disease in which flaccid paralysis is the outstanding feature and in which classic symptoms of rabies may fail to appear. A report of such a case is presented, and similar cases from the literature are reviewed.

2. Paralytic rabies runs a much less fulminating course than the ordinary form of rabies. The average duration of life in six patients with paralytic rabies was nearly twelve days.

3. Paralytic rabies may be confused with poliomyelitis. Features suggesting that the disease is not poliomyelitis are (a) disturbances in sensation (present in five of six such patients); (b) fever persisting or first appearing many days after the onset of paralysis; (c) the ultimate development, in some patients, of classic symptoms of rabies.

4. In the cases where necropsies have been performed histologic studies have usually revealed extensive degenerative or destructive changes in both the motor and sensory portions of the spinal cord. In the two cases at Vanderbilt University Hospital, Negri bodies were found not only in the spinal cord or brain of the patients, but also in the brains of rabbits inoculated with material from these patients.

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TULAREMIA IN INFANCY

With Report of a Case

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TULAREMIA is infrequently a cause of illness in infants and children. The number of reported cases in children and adolescents is small, and few cases in infancy are found in the literature. As a rule, pediatricians encounter few cases of this disease, whereas the general practitioner, especially in rural areas, has a greater opportunity for observing patients infected with tularemia. However, tularemia as a cause of illness in children is assuming a more important place in the differential diagnosis of acute febrile diseases. This is explained by a true increase in the number of infections as well as by more frequent recognition of the disease. A rather complete bibliography of tularemia in infants, children, and adolescents is appended.[1-20] In the reported cases, there are few concerning infants; the case described below adds yet another to the list which will undoubtedly increase.

It is well known that the causative organism of tularemia is *Bacterium tularense*, which is endemic among wild rabbits. With each year, new hosts for these organisms have been observed, and consequently, in history-taking, the fact that the patient has not come in contact with wild rabbits does not exclude the disease. The number and variety of hosts has become so great that the possibility of contact with the infective agent has increased tremendously. This is especially so if the tularemia organism is definitely able to pierce the intact skin or mucous membrane. Although the majority of individuals infected with tularemia have an external lesion suggesting the possibility of the disease, there may be no external physical findings, thus increasing the diagnostic difficulty. Once tularemia has been diagnosed, the plan of treatment must be considered. With the advent of the sulfonamides, several reports of their use as a means of treatment in tularemic infections have appeared in the literature[21, 22] and the antitularemia serum has been used as advocated by Foshay.[10, 22] The case reported here well illustrates the difficulties of diagnosis and also the effects produced by sulfa drugs and antitularemia serum in one child.

CASE REPORT

M. S., a 22-month-old white boy was first seen Jan. 13, 1943. Except for a slight cold, he had been apparently well until the above date, when he suddenly developed a high fever and had a prolonged generalized convulsion. When first examined, the child appeared to be acutely ill. The significant findings on examination were a profuse mucoid nasal discharge, slight inflammation of both eardrums, with absence

of the light reflex, and moderate injection of the pharynx. None of these findings appeared to be sufficient cause of the fever, and it was felt that the boy could be developing pneumonia, although there was no evidence to substantiate this viewpoint. The child was admitted to a hospital. The laboratory findings showed a red blood cell count of 3,080,000 per cubic millimeter, a hemoglobin content of 11 Gm. per 100 c.c., and a white blood cell count of 26,800 per cubic millimeter, of which 77 per cent were polymorphonuclear neutrophiles, 17 per cent small lymphocytes, 3 per cent monocytes, and 3 per cent classified as myeloblasts. Roentgen examination of the chest revealed no evidence of pulmonary or cardiac pathology.

Sulfathiazole was given orally in the amount of 1 gr. per pound of body weight per day. The temperature decreased from 105.8° F. to 98° F. overnight, and it was confidently expected that an early pneumonic process must have been present, even though it was impossible to demonstrate it. This idea was shattered by midafternoon of the day following admission to the hospital by a rise in temperature to 105.4° F. No new physical findings had developed, and no abnormality of the nasal mucosa was seen, although the profuse discharge persisted. On the fourth day after the onset of the illness, it was thought that regardless of the leucocytosis, typhoid fever should be considered, for the child lived in a region where the disease was endemic. A Widal test was done and yielded negative results. At this time, a throat culture taken on admission to the hospital reported rare gram-positive bacilli, a few gram-positive diplococci, and many gram-positive cocci identified as *Staphylococcus aureus;* the culture of the nasal discharge revealed oval bacilli staining partially gram-positive and partially gram-negative and showing bipolar staining. On January 16, four days after admission to the hospital, the sulfathiazole was discontinued and sulfadiazine begun in an identical quantity per day. The temperature which had not risen to as great a peak as it had previously began to fall by lysis and reached 98° F. on January 20. During this interval the child had not appeared to be ill except during the hours when the fever was at its height. The profuse nasal discharge continued, and there was but slight improvement in the appearance of the throat and eardrums. The child was discharged on January 20.

On January 24 the boy was returned for examination because of a recurrence of high fever. Examination at this time revealed no significant physical findings other than the marked watery nasal discharge; the slight redness of the eardrums and pharynx had disappeared. It was suggested that perhaps the child had infectious mononucleosis, although no significant lymphadenopathy was present. Blood was taken for further agglutination tests, and the child was again admitted to a hospital. A white blood cell count showed 18,600 cells per cubic millimeter, of which 47 per cent were lymphocytes, 47 per cent polymorphonuclear neutrophiles, 1 per cent basophiles, and 5 per cent monocytes; thus the possibility of infectious mononucleosis was excluded. Agglutinations of the blood serum were 4 plus positive for tularemia, negative for typhoid and paratyphoid fevers, undulant fever, Brill's disease, and infectious mononucleosis.

On January 29 15 c.c. of Lyovac antitularemia serum* were given intravenously with no immediate reaction. The temperature continued to be a septic type, and on February 5 sulfadiazine was again administered in the amount previously mentioned. During this interval the child appeared to be fairly well, and no new physical findings were encountered. On February 8, ten days after the serum was administered, the child developed several crops of urticarial wheals on the trunk and extremities; these disappeared in two days. Since there had been no apparent improvement after receiving the sulfadiazine, it was discontinued on February 8. Approximately three days later the temperature was at the normal level and after no further exacerbations the child was discharged on February 20, thirty-eight days

*H. K. Mulford Co., Philadelphia, Pa.

after the onset of his illness. The child has been free of symptoms to this time, although the nasal discharge persisted approximately two weeks after his leaving the hospital.

COMMENT

The patient referred to above was first seen following a convulsion. At the time of the examination, the temperature was found to be 105.8° F., yet the physical findings justified no diagnosis other than a moderately severe pharyngitis, rhinitis, and slight otitis media. The old adage that a disease must be suspected before it may be diagnosed is especially true in this instance.

Tularemia should always be considered in a differential diagnosis of any acute febrile disease in which the physical findings do not account for the fever or the response to the treatment is not as great as one usually experiences. Only by worrying about a patient similar to this one can the pediatrician appreciate this fact. Tularemia was not considered in this patient, and the diagnosis came about by accident. The blood was sent to the laboratory and "routine agglutinations" requested. Ordinarily the laboratory tests for typhoid, paratyphoid, undulant, and typhus fevers. However, a new laboratory technician had been employed, and as she had recently left Oklahoma where tularemia agglutinations are apparently performed routinely, this patient's serum was tested and found to be positive for tularemia, thus establishing the unsuspected diagnosis! When the technician was congratulated on having solved a difficult problem, she remarked that if the age of the patient had been on the requisition slip, the agglutination for tularemia would not have been done, as even in Oklahoma such young children were unlikely to have the disease.

The history may be of great or little value. Having obtained the diagnosis in this child's case, the parents were carefully questioned as to the possible source of infection. No rabbits had been killed, handled, or eaten by any of the family; no other members of the family had been ill. Finally it was established that the child frequently played with a large house cat which often caught and brought home wild field mice. Whether the mice or the cat could have been a possible source of infection is not known, but it is not unlikely that dogs and cats will be shown to harbor the disease a great deal more than suspected.

It can be seen from the temperature curve (Fig. 1) that the sulfathiazole had no apparent effect, and no objective change was observed. Although shortly after the sulfadiazine was given the temperature decreased, it is to be questioned whether or not this was due to the drug, for the second administration had no effect, and tularemia may apparently subside only to flare up shortly thereafter.

The use of serum has received much consideration, especially by Foshay.[10] This patient received the antitularemia serum advocated by him but with little evidence of improvement. There was also a mild

urticarial reaction ten days after the child received the serum. The question of whether this child received sufficient serum to warrant judging its value is, of course, difficult to determine. Frequently large amounts of serum must be given before beneficial results are obtained. This was not done because of the cost of the serum in this particular instance. The time of administration of the serum in relation to the duration of the illness is undoubtedly an important factor for consideration and may explain the lack of improvement of this patient. It may be presumed that serum would be of greatest value if administered at the beginning of the disease; but, because of the frequent difficulties entailed in the diagnosis of tularemia, this cannot always be done.

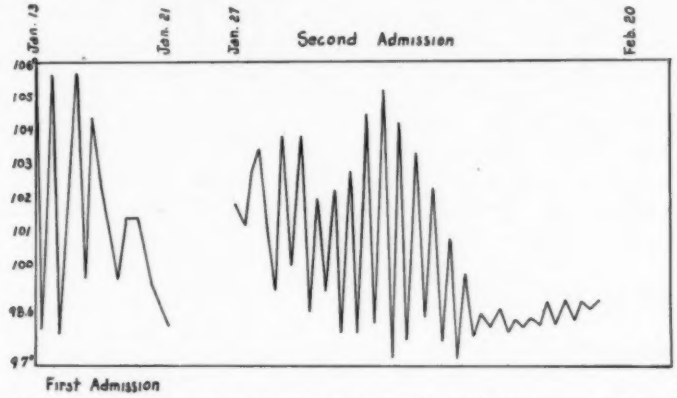

Fig. 1.—Temperature curve of patient M. S. during both admissions to hospital.

Thus tularemia remains a disease especially difficult to diagnose clinically in young infants and children, a disease for which truly adequate specific therapy has not yet been produced, but, fortunately, a disease of low mortality.

CONCLUSIONS

1. Tularemia must be suspected in any acute febrile illness regardless of the absence of physical signs or history of a possible source of infection.

2. The sulfa drugs were of no apparent value in the treatment of tularemia in the case reported above.

3. Antitularemia serum as advocated by Foshay was of no objective value in relieving the symptoms or in shortening the course of the disease in this patient.

4. All laboratories should test blood samples for tularemia when "routine agglutinations" are requested.

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115 S. UNION STREET

WHOOPING COUGH CONTROL

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THE writing of this paper has been deemed necessary in view of the laissez faire attitude of many health departments with respect to the prophylaxis and control of whooping cough. This is evidenced by a recent statement of the commissioner of health of a large city to the effect that whooping cough control is impracticable since infection has occurred by the time the diagnosis is made.

The high morbidity rates of whooping cough are evidenced by Collins' survey in 1924, in which he found that in 30,000 school children in eastern and southern areas of the United States, 56.8 per cent of all children had had pertussis by the age of 5 years and 73.5 per cent, by the seventeenth year. The high infectivity rate in familial exposures was shown by Culotta, Dominick, and Harrison,[1] who found that in nineteen families in which there was a case of whooping cough, of twenty-eight susceptible children, all developed the disease. The high mortality rate is demonstrated by the 285 deaths in 31,228 cases in New York City in the five-year period 1936-1940. Incidentally, Emerson[2] showed that for cities with a population over 500,000 the case fatality per cent ranged from 0.7 to 4.3 per cent, with New York City having the highest percentage, 4.3 per cent. Garvin[3] recently compared the tables of incidence per 100,000 population in children under 5 years of age in two contiguous cities. Cleveland, with a population of 1,000,000, in which no whooping cough vaccination is offered, is estimated as immunizing only 10 per cent of susceptible children. Shaker Heights, with a population of 25,000, is estimated as immunizing 75 per cent of the infants during the last four to five years. The table of incidence shows no drop in the Cleveland rate and a drop of from 365 in 1934 to 182, 54, 74, 21, and 45 for the next five years in the Shaker Heights rates.

The necessity for control is then evident. I shall now discuss ad seriatim the objections raised to the different elements of the projected program for whooping cough control from a public health standpoint.

The objections to routine prophylaxis or immunization of well children in the second half of the first year of life, by means of vaccine injections, stem from two mistaken ideas: first, that more time is needed to settle the question of the value of vaccine prophylaxis, and, second, that large scale vaccination would be too expensive. Since the use of large doses of vaccine in prophylaxis as originally advocated by Madsen[4] and popularized by Sauer[4] is now at least fifteen years old, and

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since every recent review[4] of the subject admits a striking effect of vaccine immunization in reducing both the attack rate and the communicability rate in vaccinated children, as compared with adequate controls, surely it is time for health departments to be convinced. The main exponent of the virus theory[5] has retracted his viewpoint and the poor results of another study[6] have been explained by their use of washed vaccine. The great majority of pediatricians in this country are convinced of the efficacy of routine prophylaxis by whooping cough vaccine. The second objection to routine prophylaxis is that growing the organisms on a human blood medium makes large scale production impracticable. But Mishulow,[7] working with a sheep blood vaccine, found the quantity in the vaccine far too small to produce sensitization, and, working with bovine blood vaccine, I[8] could get no evidences of sensitization in a large series. If commercial companies can produce a vaccine costing about 75 cents per complete immunization, it seems probable that the health department laboratories could bring the cost down to 30 cents—truly not an expensive figure.

The second necessity in a whooping cough control program would be provision of diagnostic aids so that early diagnosis could result in effective quarantine and attempt at prophylaxis of susceptible contacts. The conservative objection to this program is that diagnosis is so difficult that by the time the child is known to have whooping cough, the short incubation period is over and contacts are already ill. But the incubation period is not so short; Lawson[9] estimated it as 13.05 ± 7.6 days, and Kendrick and Eldering,[10] as 15.4 ± 1.3 days. If, then, all afebrile coughs of even a few days' duration are regarded with suspicion and the mother is instructed to quarantine the ill child until cultures are reported, many infections can be prevented. Sauer's experiences in Evanston and my own experiences in a special whooping cough clinic in the Bronx are very definite on this point.

The common objection to the provision of diagnostic aids by health departments is also the expense of keeping a constant supply of cough plates on Bordet-Gengou medium available. Sauer's[11] use of culture boxes which require very little medium and are easily transported is very practicable. The boxes are kept only two weeks because they usually darken and the surface becomes dry. Since this is extravagant of human blood, substitution of sheep blood, as by Brooks, Bradford, and Berry,[12] or of bovine blood, as by Jamieson,[13] or of horse blood, as by Miller, Leach, Saito, and Humber,[14] should prove less expensive. Percentages of recovery of the organism in the catarrhal stage vary from Bradford and Slavin's[15] 25 per cent to Sauer and Hambrecht's[16] 99 per cent. If nasopharyngeal and throat swabs are taken in addition to throat cultures, especially in infants, these results can be improved. Thus, using the Bradford and Slavin technique of cotton wound on the end of a thin flexible copper wire, passed through the nose until it

reached the posterior end of the pharynx, Miller, Leach, Saito, and Humber[14] obtained a higher percentage of positive cultures than by the cough plate. Brooks, Bradford, and Berry[12] kept the cotton swab moist by suspension in a test tube containing a bit of rubber sponge wet with 0.85 per cent solution of sodium chloride, and by keeping a rubber stopper on the test tube. Of seventeen swabs, fifteen were positive after being held at room temperature for twenty-four hours in this fashion. To recapitulate, what health departments would be expected to supply is cotton swabs on a flexible wire in a rubber-stoppered test tube, and, in addition, in suitable cases, cough plates or culture boxes with sheep blood or bovine blood—Bordet-Gengou medium. In a very large percentage of cases, a definite diagnosis could be made by the third or fourth day of the cough. Only a minimal expense would be involved in providing these diagnostic aids to the practicing physician and the hospital clinics.

The third necessity in a whooping cough control program would be the provision of some method of prophylaxis for exposed children. When a definite bacteriologic diagnosis of whooping cough has been made, the home should be placarded, the child should be forced to wear a yellow arm band, and susceptible siblings should be excluded from school and public gatherings for at least two weeks after their last exposure to the disease. In New York City, for instance, whooping cough contacts are not excluded from school, precisely in the most contagious, catarrhal stage. In addition, children under 3 years of age who are sibling contacts should receive convalescent or hyperimmune human serum in appropriate doses. The studies of McGuiness, Bradford, and Armstrong,[17] as well as my own[18] and a number of other controlled studies have been so striking that we can safely assume that from 73 to 85 per cent of the contacts so injected will not develop whooping cough. Thus, McGuiness, Stokes, and Armstrong,[19] using vacuum-dried hyperimmune whooping cough serum* in 215 cases following exposures to siblings, report that 78 per cent failed to contract the disease at all, 10.3 per cent contracted a very mild form with no whooping or vomiting, 5.6 per cent had a mild form with some whoop but no vomiting, and 6 per cent had a typical attack of whooping cough. They secured their best results when the serum was administered within the first week after the initial exposure.

I recognize that the expense involved in this serum is too great for the average health department to bear, but a fair number of cities now have serum exchanges, and provision may be possible for infants under 1 year of age. At the least, private physicians should be informed of the possibility of the passive immunization. The use of vaccine prophylaxis for contacts as reported by Schermerhorn[20] must still be regarded

*This vacuum-dried, "lyophile" serum is obtainable from the Philadelphia Serum Exchange at the Children's Hospital of Philadelphia.

as subjudice, and the objections to the use of rabbit immune serum on theoretical grounds of sensitization are very real.

To summarize, the control of whooping cough by a public health program is both necessary and practicable at the present time. Health departments should include routine prophylaxis for well children, cough plates, nasopharyngeal and throat swabs for diagnosis, and provisions for serum prophylaxis for contacts.

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NIEMANN-PICK DISEASE

(Acute Idiopathetic Xanthomatosis, Phosphatide Lipoidosis, Lipoid Cell Splenomegaly—Niemann Type)

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NIEMANN-PICK disease is considered a rare and unusual entity. For this reason a case recently seen at The Children's Memorial Hospital will be presented with a review of the literature.

CASE REPORT

F. A., a white female, was born Jan. 30, 1943, of Italian and English-Irish parents. The birth weight was 8 pounds, 8 ounces. She was admitted to the Children's Memorial Hospital April 13, 1943, with symptoms of constipation, cyanosis, swollen feet, projectile vomiting, and weight loss. The mother had a normal pregnancy. Labor lasted two and one-half hours with constant, steady pains. There was some difficulty at the time of delivery; the child was "blue" at first and her face was swollen and discolored. The swelling was still present at the time of her admission to the hospital. According to the mother, the child had had only one yellow stool every third day with the aid of a glycerine suppository. She began to vomit projectilely several times daily the week before admission. She had gained only one ounce since birth. Three days before admission the infant developed a cough without fever, and the day before admission her feet began to swell. The child had received breast milk supplemented with evaporated milk. Later this was changed to homogenized milk with dextrimaltose and water. She also received haliver oil with viosterol, 10 drops, and one ounce of orange or prune juice daily.

The family history revealed the mother to have had a positive blood test for syphilis at the age of 17 years. She received treatment and all subsequent tests were negative. She was 33 years of age when the child was born. The father was 47 years of age and in good health. There was one sibling, 7 years of age, who was entirely normal.

Examination at the time of hospital admission revealed a 10-week-old girl with marked pallor and cyanosis. The eyes were puffy and the bridge of the nose was depressed. There was purulent material in both eyes and throat. The facies suggested cretinism, but the tongue was not thickened and did not protrude. There was decreased resonance over the left chest posteriorly, and inconstant, moist, medium and fine râles in the same area. The heart size could not be outlined by percussion; a tachycardia was present, but no murmurs were heard. The abdomen was soft and the liver was palpated 7 cm. below the costal margin. The only additional abnormal finding was edema of the legs and feet.

The erythrocyte count was 4,050,000 per cubic millimeter with 11.6 Gm. hemoglobin. The leucocytes numbered 20,400 per cubic millimeter with 38 per cent polymorphonuclear leucocytes, 58 per cent lymphocytes, 4 per cent monocytes, and approximately 13 per cent nucleated red blood cells. Examination of a second blood smear showed 30 per cent of the lymphocytes to be vacuolated. Nonprotein nitrogen

From the Otho S. A. Sprague Memorial Institute and The Children's Memorial Hospital.

Fig. 1.

Fig. 2.

Fig. 1.—Photograph shows the Mongoloid features and enlargement of the liver and spleen.

Fig. 2.—Anteroposterior view of one upper and both lower extremities shows faint visualization of the periosteum of the shafts of some of the long bones. The bones show coarse trabeculation and the metaphyseal lines fade slightly.

was 37 mg. per cent; cholesterol (serum), 132 mg. per cent; and total protein, 5.5 per cent. The tuberculin and Wassermann tests were negative.

Following admission, the infant's temperature rose to 102° F. Her eyes were treated with 5 per cent sulfathiazole ophthalmic ointment, and nose drops, ½ per cent ephedrine, were administered three times daily. She was given 1 drop of atropine (1:1000) twenty minutes before each feeding and ⅛ gr. of thyroid extract three times daily.

The child died thirty hours after admission. A tentative diagnosis of congenital heart disease and possible hypothyroidism was made.

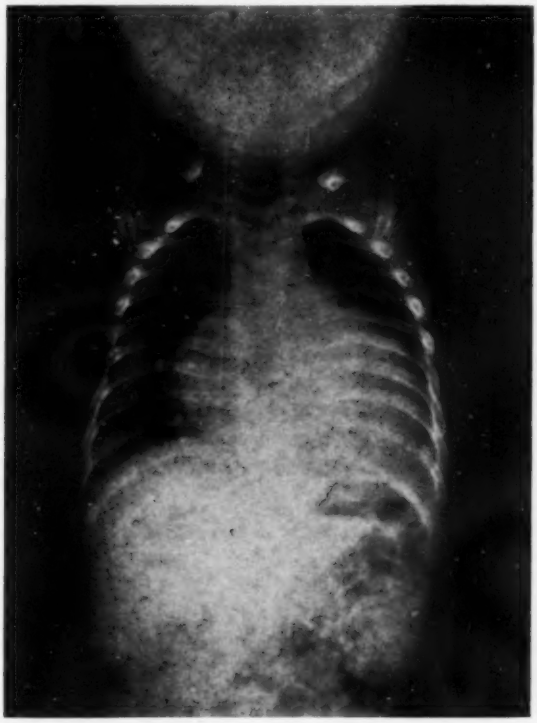

Fig. 3.—The heart is at least 100 per cent enlarged, mostly to the left. There is a prominent left auriculoventricular salient. The shape of the heart suggests that the shadow is heart rather than pericardial fluid.

AUTOPSY REPORT

Gross Examination.—Post-mortem examination was made four hours after death. The body was moderately pale, weighed 8½ pounds, was twenty-four inches long, and was well proportioned but small. There was pitting edema of the face and forehead. The facies was cretin-like; the bridge of the nose was sunken. The anterior and posterior fontanels were open, the former measuring 4 by 5 cm., and the sagittal suture line was widely separated. The autopsy was limited to the trunk with all organs to be returned to the body. When the sternum was removed, the heart was found to be moderately enlarged, weighing 58 Gm. (average normal, 23 Gm.). The enlargement was due to a generalized dilatation and hypertrophy of the left ventricle. The lungs were rather white and crepitant with evidence of passive hyperemia dependently. Together they weighed 102 Gm. (average normal, 62 Gm.).

The liver was a yellow-tan color with patches of purple-red. It extended from the fourth rib on the right to a point 5 cm. below the costal margin and weighed 244 Gm. (average normal, 140 Gm.). On section the liver became convex, felt very greasy, and had a yellow-tan color.

The spleen was firm, a deep red-purple color, and weighed 50 Gm. (average normal, 14 Gm.). Its capsule was smooth. The parenchyma was of a homogeneous red-brown color and the Malpighian corpuscles could not be seen.

The kidneys were essentially normal and together weighed 52 Gm. (average normal, 40 Gm.). Their capsules stripped with ease and there was only slight evidence of fetal lobulation.

The adrenals, pancreas, lymph nodes, generative system, and gastroenteric tract were normal.

Microscopic Examination.—Technique: Six hours after death the tissues were placed in Zenker's solution and in 10 per cent formalin. A complete series of Zenker-fixed tissue was embedded in paraffin and stained with hematoxylin and eosin. Frozen sections of liver were also stained with sudan IV or scharlach R which revealed no neutral fat or cholesterol; Mallory's stain brought out the fat droplets nicely but did not show the fibrillar-like arrangement as is seen in Gaucher's disease; iron hematoxylin made the lipoid material a granular gray-black; Nile blue sulfate stain did not bring out the fatty material very well, but the "foam cells" had a hazy, granular appearance.

Special stains were also used on various tissues which will be mentioned later.

Liver: The general structure of the liver had been greatly disturbed. The liver cord formation was broken up and the hepatic cells, with hematoxylin and eosin stain, were swollen and filled with irregular fatlike globules, and some contained a faint pink granular material. The hepatic cells, instead of being polygonal, were irregularly round or oval. The round nucleus with one or two nucleoli was found either in the middle or at the periphery of the cells, and its membrane or condensed protoplasm stained a blue-purple. A small percentage of Kupffer's cells also contained this foamy, lipoidlike material. The sinusoids were twisted due to the fact that they wound about the foam cells. Glisson's capsule, the bile ducts, veins, and arteries were relatively normal. With sudan IV (scarlet red) the foam cells were colorless or had a faint green hue instead of a scarlet color as is seen with fat. With Mallory's aniline blue only the fine reticular fibers took on a stain. Other sections were stained with Nile blue sulfate to demonstrate free fatty acids (blue) and neutralized fats (red), but the tissue took on a yellow-green color. Iron hematoxylin stained the entire tissue a deep blue even after much washing with tap water. A section taken from an injected bleb on the liver again revealed the foam cells, no liver cords, and marked myelopoiesis. It was truly a hepatoma. It should be stated that Mallory's stain brought out the foamy appearance nicely but did not show the fibrillar-like arrangement as is seen in Gaucher's disease. With the Lorrain Smith-Dietrich method the lipoid material did not stain blue-black as it should.

Lungs: The pleura appeared normal, but the subpleural connective tissue was thickened and edematous. Many alveoli were collapsed and others were filled with large, pale, vacuolated cells similar to those described above. It was of interest to note that the lining cells of the alveoli also contained the same type of foam cell. It is also true that this child had a lipoid cell pneumonia.

Pancreas: Section through the body of the pancreas showed about two-thirds of the acini to be involved by an infiltration of this lipid material. With hematoxylin and eosin stain the islets were not affected.

Spleen: The germinal centers of the spleen blended with the red pulp and were not sharply defined as is usually seen. Both the follicles and red pulp contained

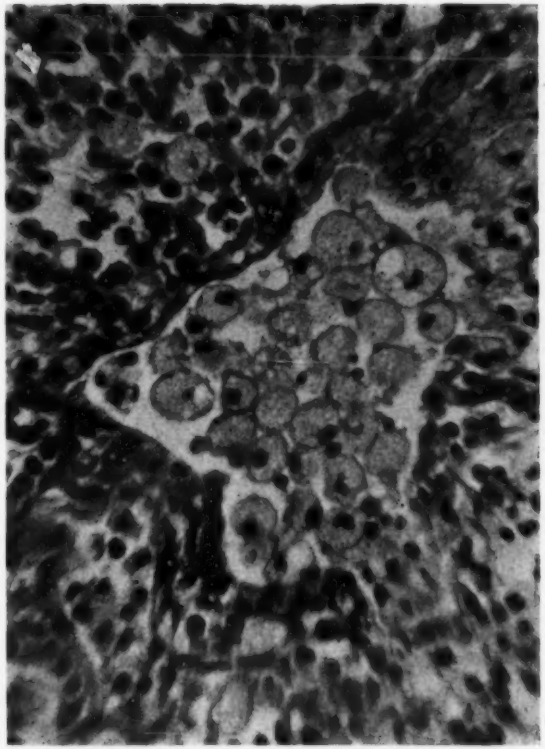

Fig. 4.

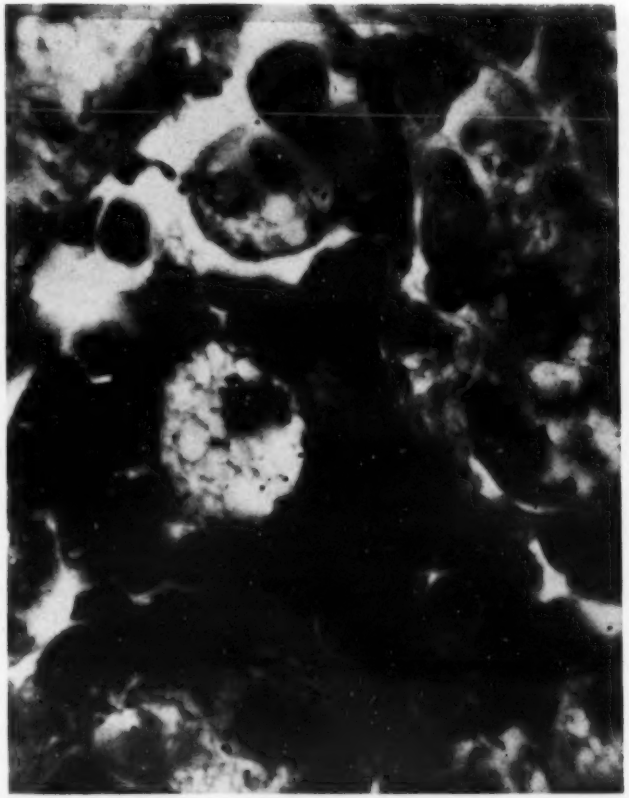

Fig. 5.

Fig. 4.—Photomicrograph of a section of lung showing foam cells in an alveolus (×264).
Fig. 5.—Photomicrograph of a section of liver showing fat laden cells (×1000).

these foam cells, but the involvement was not as dramatic as that of the liver. The cells involved were probably reticulocytes.

Thymus: The many lobules of the thymus visualized nicely, and the cortex with its masses of lymphocytes or thymocytes was sharply separated from the medulla with many large Hassall's corpuscles and reticular cells. Scattered throughout the cortex and medulla were numerous "foam cells."

Kidney: Precipitated protein was present in the tubules. The glomeruli were greatly enlarged, all being from one to one and one-half times larger than normal. The cells of the glomerular epithelium were colorless with hematoxylin and eosin stain and their nuclei were dark and essentially normal, but only a few of these large, pale cells had a foamy structure.

Fig. 6.—Photomicrograph of a section of bone revealing replacement of normal cortex on left by foam cells. The same fat laden cells are seen in the narrow cavity (×60).

Bone: First, studying the cartilage-shaft junction, a rachitic zone was found with a large amount of osteoid tissue adjacent to the shaft and with irregular columns of cartilage cells projecting into the osteoid tissue. Second, the normal appearing cortex was absent and the same previously described foam cells lined the periosteum. The fat laden cells were seen throughout the marrow cavity, and the bone involvement was almost as severe as that of the liver. There was no hemorrhage or pigmentation seen, no "fracture of bony spicules" to make one think scurvy was present, and new bone was being laid down beneath the periosteum.

REVIEW OF LITERATURE

With fifty-nine proved cases of Niemann-Pick disease in the literature since 1914, this condition cannot be considered one of extreme rarity. Three additional cases from personal communications are also recorded which increases the total number of known cases to sixty-two. The question as to whether this condition is familial is equivocal, but with more cases being reported it appears that this may be a characteristic. The following have definite histories of more than one instance in the family: Knox, Wahl, and Schmeisser's[33] two cases; the case of Dienst[17] and that of Stransky;[58] Nordmann's[43] case and that of Corcan, Oberling, and Dienst;[16] Winter[66] reported two cases of siblings; Kramer's[35] case in 1928, and the two cases of Merksamer and Kramer[39] in 1939 were siblings; Maurer[38] reported siblings in 1941; and Freudenberg[25] found this condition in identical twins. Thus, fifteen of fifty-nine cases, or 25 per cent, were definitely familial. With probable familial histories (Siegmund,[55] Dienst and Hamperl,[18] Hamburger,[28] and Berman[10]) the percentage is even higher—roughly, 32 per cent.

Case reports in the American and foreign literature reveal the sex distribution to be almost equal—thirty females and twenty-six males (in three cases the sex was not mentioned).

Thirty of the patients were Hebrew, eighteen were not Hebrew; in eleven there was no mention of race.

The earliest onset of this condition dated back to birth. All children died before they were 3 years old, the oldest at 30 months.

Post-mortem examinations or biopsies were done on forty-seven of the fifty-nine deceased patients.

Acute idiopathetic xanthomatosis, phosphatide lipoidosis, lipoid cell splenomegaly—Niemann type, or Niemann-Pick disease, is a disease of infancy found mainly in the Jewish race. It is probably congenital, affects the sexes equally, and is characterized by enlargement of the liver, spleen, and frequently the lymph nodes. The infant's development is retarded, and feeding is undertaken with difficulty. Examination may reveal edema, with or without ascites; enlargement of the abdomen, due to the organs mentioned above and fluid; a brown-yellow pigmentation of the skin; a Mongoloid appearance; and emaciation. The blood picture shows a secondary anemia and frequently vacuolated mononuclear cells. The presence of a cherry red spot in the region of the macula in both this condition and Tay-Sachs disease brings up a controversial point. Sachs[51] stated the two diseases were entirely different. He felt that in Niemann-Pick disease the metabolic disorder affected the entire body and in Tay-Sachs disease, only the nervous system. Hassin,[29] in his report in 1930, and Epstein,[20] in 1935, likewise considered the two conditions as different entities. With combined mental and physical deterioration, death results from either cachexia or an intercurrent infection.

Niemann's[42] original paper on this subject was first printed in 1914. Later, in 1922, Pick[46] carefully and completely showed the difference between this disease and Gaucher's disease and called this condition "lipoid cells splenomegaly—Niemann type."

Niemann's patient in 1914 was a girl whose parents were Jewish; she had been sick since her second month of life. She was first seen by him at the age of 17 months. The infant had difficulty in eating and did not develop normally. Her condition gradually became worse, and her abdomen grew larger. She was referred to the Children's Clinic of the Berlin University. Her liver and spleen were enormous, anasarca was present, the skin was pale, the blood picture was normal, but the Wassermann reaction was positive. The child developed an irregular fever, a diarrhea, and died at the age of 18 months. Autopsy revealed no syphilis, a very large, yellow-white spleen, and an enormous, fatty liver. Microscopic examination of the organs showed a replacement of the normal parenchyma by vacuolated cells which were irregular and large. The difference between this and Gaucher's disease was the early age of onset and the rapid course. It was therefore called "an unknown disease picture."

The pathogenesis of this disease is still open to investigation. Niemann believed it to be a disturbance in fat metabolism and this seems to be true. Pick[44] stated, in his paper in 1933, that the storage cells covered a wider range than did those of the reticulo-endothelial system and spread into all tissues. To quote him, "the pathogenesis revolves itself upon a primary metabolic disturbance which leads to an overloading of the blood stream and tissues with lipids, especially the phosphatids. At the same time a marked disappearance of the stored neutral fat takes place. The foreign material in the blood stream and tissue fluids first of all mobilizes the entire histiocytic apparatus, mainly the spleen, the liver, the lymph nodes, and the bone marrow." The real cause of the faulty metabolism is still not understood. Chargaff,[14] of Columbia University, reported in detail the results of his analysis of the spleen in a case of Niemann-Pick disease. His results confirm the reports of Klenk, Epstein, Lorenz, and others, that there is an increase in the amount of sphingomyelin in the various organs in Niemann-Pick disease and chemical analysis can differentiate this condition from Gaucher's and Schüller-Christian's disease. In 1927 and 1928 Pick and Bielschowsky and Bielschowsky alone studied postmortem material from cases of Niemann-Pick disease and amaurotic family idiocy. To quote from the paper of Merksamer and Kramer,[39] "As the result of their studies, they [Pick and Bielschowsky] suggested an intimate relationship between the two conditions. The degenerative changes in the central nervous system that are seen in Tay-Sachs disease are also present in Niemann-Pick disease."

DIFFERENTIAL DIAGNOSIS

Of the conditions to be differentiated from Niemann-Pick disease, only two need be carefully considered—Gaucher's disease and Tay-Sachs disease. The other conditions are mentioned to complete the discussion.

Gaucher's Disease.—Gaucher's disease is usually characterized first by a very large spleen, a mild anemia, and a well-appearing child. In the second stage the liver enlarges, there is progressive anemia, and a leucopenia develops. Finally ecchymosis, bruises, and tarry stools are noticed. There may be pains along the bones. The superficial nodes are rarely enlarged, the skin becomes a yellow-brown, and yellow wedge-shaped thickenings of the ocular conjunctivae are noticed. Gaucher's cells have never been demonstrated in the blood, and the thrombopenia which develops returns to normal after splenectomy. The disease is found in early childhood and not in infancy. Osteoporosis is found later with cystic changes and thinning of the cortex of the long bones. The finding of Gaucher's cells in biopsy of a lymph node or with splenectomy is the only positive proof of the presence of the disease.

The acute form of Gaucher's disease is similar to the above description except that it attacks the infant; cellular involvement extends beyond the lymph nodes, spleen, liver, and bones and also affects the lungs and enteric tract. The central nervous system is involved and the child becomes hypertonic. Death occurs shortly thereafter.

TABLE I*

	GAUCHER'S DISEASE (NEUROLOGIC FORM)	NIEMANN-PICK DISEASE
1. Age of onset	First six months	May begin after six months
2. Race	No special predisposition	Jewish race 50 per cent
3. General appearance	Usually no discoloration; expression of sadness	Mongoloid facies frequent; yellow, waxy skin
4. Neurologic signs	Hypertonia; strabismus; laryngeal spasm; dysphagia; catatonia	Usually hypotonia; no pseudobulbar syndrome
5. Liver and spleen	Splenomegaly usually precedes hepatomegaly	Opposite may be found
6. Fundi	Negative; occasionally temporal pallor	Cherry red spot at macula lutea frequent
7. Blood	Slight anemia and leucopenia; no morphologic changes	More severe anemia with leucocytosis; vacuoles in cytoplasm of lymphocytes frequent
8. Chemistry	Normal or low blood cholesterol and fatty acids	All these are definitely elevated
9. Biopsy	Relatively scarce presence of Gaucher's cells in sternal marrow but numerous in spleen	Relatively numerous Niemann-Pick cells in all aspirated tissues

*From Aballi and Kato.[1]

TABLE II*

AUTHOR	YEAR	ONSET	DEATH	NATIONALITY AND/OR RELIGION	SEX	AUTOPSY	DIAGNOSIS
Niemann	1914	2 mo.	17 mo.	Polish	F.	Yes	"An unknown disease picture"
Knox, Wahl, and Schmiesser	1916	9 mo.	11 mo.	Jewish	F.	Yes	Gaucher's disease
Knox, Wahl, and Schmiesser	1916	5 mo.	15 mo.	Jewish	F.	Yes	Gaucher's disease
Siegmund	1921	1 mo.	9 mo.	Jewish	F.	Yes	Gaucher's disease
Fahr and Stamm	1923		(age 3 mo.)	Jewish	M.	Yes	Gaucher's disease
Bloom	1925		(age 16 mo.)	Jewish	F.	Yes	Niemann-Pick disease
Bloom	1925	7 mo.	21 mo.	Jewish	F.	Biopsy of spleen and liver	Niemann-Pick disease
Bloom	1925		(age 7 mo.)	Jewish	M.	Yes	Niemann-Pick disease
Henschen	1926	9 mo.	11 mo.	Jewish	M.	Yes	Niemann-Pick disease
Schiff	1926	3 mo.	------	--------	M.	No	----------
Corcan, Oberling, and Dienst	1926	-----	7 mo.	Christian	M.	Yes	Niemann-Pick disease
Dienst and Hamperl	1927		(age 5½ mo.)	--------	M.	Yes	Niemann-Pick disease
Hamburger	1927	1 mo.	14 mo.	Jewish	F.	Yes	Niemann-Pick disease and amaurotic iodicy
Lowy	1927	3 mo.	3½ yr.	Jewish	--	No	----------
Abt and Bloom	1928	6 mo.	17 mo.	Jewish	F.	Biopsy of spleen	Niemann-Pick disease
Berman	1928	2 mo.	15 mo.	Jewish	F.	Yes	Niemann-Pick disease
Kramer	1928	4 mo.	14 mo.	Jewish	F.	Biopsy of spleen	Niemann-Pick disease
Chwalibogowski and Schusterówna	1929	3½ mo.	18½ mo.	Jewish	F.	Yes	Niemann-Pick disease
Dienst	1929	3 mo.	7 mo.	Catholic	F.	Yes	Niemann-Pick disease
Schmitz and Thoenes	1929	-----	20 mo.	Not Jewish	M.	Yes	Niemann-Pick disease
Baty	1930	4 mo.	10 mo.	Jewish	F.	Yes	Niemann-Pick disease
Meyenburg	1930	6 mo.	12 mo.	Not Jewish	M.	Yes	Niemann-Pick disease
Smetana	1930	Birth	20 mo.	Jewish	F.	Yes	Niemann-Pick disease
Sobotka, Epstein, and Lichtenstein	1930	6 mo.	11 mo.	Jewish	F.	Yes	Niemann-Pick disease
Stransky	1930	-----	------	Not Jewish	M.	No	Niemann-Pick disease
Goldstein and Wexler	1931	10 mo.	15 mo.	Jewish	F.	Yes	Niemann-Pick disease
Poncher and Hassin	1931	1 mo.	18 mo.	Jewish	M.	Yes	Niemann-Pick disease
			(Complete study of brain of Poncher's patient by Hassin in 1930)				
Shaferstein	1931	-----	1 yr.	Jewish	M.	Yes	Niemann-Pick disease
Druss	1931	10 mo.	13 mo.	Jewish	F	Yes	Niemann-Pick disease

Wascowitz	1931	6½ mo.	18 mo.	Jewish	F.	----	----------
Fisher	1932	2 mo.	------	Jewish	F.	Biopsy of spleen	Niemann-Pick disease
Knox and Ramsey	1932	18 mo.	28 mo.	Austrian	M.	Yes	Niemann-Pick disease
Winter	1932	9 mo.	17 mo.	Jewish	F.	Yes	Niemann-Pick disease
Winter	1932	3 mo.	8 mo.	Jewish	F.	No	Gaucher's disease (?)
Nordmann	1933	7 mo.	12 mo.	Christian	M.	Yes	Niemann-Pick disease
Nordmann	1933	6 mo.	------	Not Jewish	M.	No	Niemann-Pick disease
Pounders	1933	6 mo.	11 mo.	Not Jewish	M.	No	Niemann-Pick disease
Tow and Wechsler	1933	Birth	9 mo.	Italian	F.	Yes	Niemann-Pick disease
van Bogaert	1934	7 mo.	17½ mo.	Jewish	F.	Yes	Niemann-Pick disease
Vickery	1934	7 mo.	11 mo.	--------	F.	Yes	Niemann-Pick disease
Baumann	1935	10 mo.	27 mo.	Not Jewish	F.	Yes	Niemann-Pick disease
			(Baumann, Esser, Klein, Schiedegger again in 1936)				
Espinós, Uribes, and Viliplana	1936	2 mo.	30 mo.	Not Jewish	F.	Yes	Niemann-Pick disease
Guccione	1936	8 mo.	18 mo.	Not Jewish	M.	Yes	Niemann-Pick disease
Tropp and Eckardt	1936	-----	------	--------	--	----	----------
Angel and McConnell	1937	8 mo.	21 mo.	--------	F.	Biopsy of spleen	Niemann-Pick disease
Freudenberg	1937	-----	17 mo.	Irish	M.	Bone examination	Niemann-Pick disease
Freudenberg	1937	-----	19 mo.	Irish	M.	Bone examination	Niemann-Pick disease
Tokugawa	1937	5 mo.	17 mo.	--------	M.	Yes	Niemann-Pick disease
Hora	1937	10 mo.	25 mo.	Not Jewish	--	Yes	Niemann-Pick disease
Merksamer and Kramer	1939	1½ mo.	4½ mo.	Jewish	F.	Yes	Niemann-Pick disease
Merksamer and Kramer	1939	4½ mo.	22 mo.	Jewish	M.	No	Niemann-Pick disease
Lignac and Teunissen	1938	----	6 mo.	Not Jewish	M.	Yes	Niemann-Pick disease
Wood	1938	8 mo.	14 mo.	--------	F.	Yes	Niemann-Pick disease
Armand-Delille, Abricosoff, Jousse-met-Lefèvre, and Pittulaga	1940	17 mo.	------	--------	M.	No	Niemann-Pick disease
Reeves and Anderson	1941	Birth	9 mo.	Jewish	M.	Yes	Niemann-Pick disease
Maurer	1941	6 to 11 mo.	21 mo.	--------	F.	Yes	Niemann-Pick disease
Maurer	1941	3 mo.	21 mo.	Jewish	M.	No	Niemann-Pick disease
Maurer	1941	4½ mo.	7½ mo.	--------	M.	Yes	Niemann-Pick disease
Maurer	1941	8 mo.	11½ mo.	--------	F.	Yes	Niemann-Pick disease

*Portion of this table was taken from F. R. B. Atkinson.[5]

Tay-Sachs Disease.—In Tay-Sachs disease no visceral symptoms are found and signs and symptoms usually set in at from 4 to 8 months of age. The child cannot sit up, will not follow objects with his eyes, and is unable to control his head. There is weight loss. A cherry red spot surrounded by a gray zone in the fovea is seen. The child becomes spastic, helpless, and blind. There is a bilateral Babinski sign. Convulsions develop, contractures and emaciation set in, and death follows shortly thereafter. Histologically the ganglion cells are swollen, their cytoplasm is granular, the nuclei are pushed toward the periphery, and small lipoid droplets are seen in the cytoplasm. Both Tay-Sachs disease and Niemann-Pick disease reveal phospholipids within the involved cells. (Ford.[24])

Hand-Christian-Schüller's Disease.—Hand-Christian-Schüller's disease, a familial disorder of lipoid metabolism, is thought by many to be the chronic form of Niemann-Pick disease. The symptoms in a fully developed case are marked bony defects, especially of the skull, exophthalmus, diabetes insipidus, yellow color to the skin, and sometimes enlargement of the spleen and liver. The characteristic cell is pale, round, or oval; much cytoplasm is present and loaded with small fat droplets which are mostly cholesterol and some phospholipids. Later in the disease plasma cells, leucocytes, lymphocytes, and eosinophiles are found in what may be called granulation tissue.

Letterer-Siwe's Disease.—Letterer-Siwe's disease is much like Hand-Christian-Schüller's disease, but in contradistinction there is no lipoid material in the endothelial cells. According to Siwe, there is enlargement of the liver and spleen; a hemorrhagic diathesis; generalized enlargement of the lymph nodes; secondary anemia with a normal leucocyte count; the disease attacks infants and the young, is not hereditary or familial, and always has a fatal prognosis; localized skeletal defects are present; and there is hyperplasia of the reticulo-endothelial system without lipoid material in the cells. Wallgren[64] is a firm believer that the two diseases are the same except that Letterer-Siwe's disease is fatal and strikes the infant; that it is the malignant form of Hand-Christian-Schüller's disease of later childhood.

Syphilis.—The visceral type of syphilis is ruled out by a negative serology in the child and parents, the course of the disease, and the absence of other signs of syphilis.

Malaria and Kala-Azar.—Malaria and kala-azar are ruled out by the absence of specific parasites in the blood and by a febrile course.

Hanot's Hypertrophic Biliary Cirrhosis.—In Hanot's hypertrophic biliary cirrhosis one finds marked jaundice and an enlarged spleen. Late, infra-red photography will disclose collateral circulation, barium will reveal esophageal varices, and van den Bergh's reaction will be direct. Still later, the enlarged liver will become smaller.

Tuberculosis.—Tuberculosis is ruled out by x-ray, history, course, and specific skin test.

Congenital Hemolytic Anemia.—Congenital hemolytic anemia is usually accompanied by jaundice, urobilinemia, marked enlargement of the spleen, abnormal fragility of the red blood cells, indirect van den Bergh's reaction, and slightly enlarged or normal liver. There is improvement or cure with splenectomy.

SUMMARY AND CONCLUSIONS

The literature on Niemann-Pick disease has been reviewed and a new case reported.

The patient was a 10-week-old girl, of Italian and English-Irish parentage, whose symptoms started at birth and terminated seventy-three days later. An autopsy was performed on the trunk and findings are presented in this paper. Dr. Smith Freeman, of Northwestern University, analyzed formalin-fixed liver and his results expressed in terms of dry liver were as follows:

Total fat	10.0	Gm. per cent
Total cholesterol	0.818	Gm.
		or
	8.2	per cent of total fat
Lipoid phosphorus expressed as lecithin	3.78	Gm. per cent
		or
	38.0	per cent of total fat

The normal range for liver fat in human subjects according to Ralli, Rubin, and Rinzler[49] is essentially the same as that indicated above.

With this report, sixty proved cases of Niemann-Pick disease can be found in the literature, thirty-two affecting females and twenty-six males. Thirty of the sixty with the disease were in the Jewish race, and 32 per cent had a familial history.

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American Academy of Pediatrics

Proceedings

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., Nov. 5, 1942

Round Table Discussion on Sinusitis in Children

Chairman: Dr. W. Likely Simpson, Memphis, Tenn.
Associates: Dr. O. E. Van Alyea, Chicago, Ill.
Dr. French Hansel, St. Louis, Mo.
Dr. Edgar J. Huenekens, Minneapolis, Minn.
Dr. Paul Holinger, Chicago, Ill.
Dr. George S. Livingston, Chicago, Ill.
Secretaries: Lee Bivings, M. D., Atlanta, Ga.
Maurice J. Lonsway, M.D., St. Louis, Mo.
James E. Dyson, M.D., Des Moines, Ia.
Frederick C. Rodda, M.D., Minneapolis, Minn.

Local Complications of Accessory Sinus Disease in Children

W. Likely Simpson, M.D., Memphis

Only local complications arising from infection of the accessory sinuses of the nose will be considered here. Regarding meningitis, the operative treatment of the affected sinuses and not the treatment of the meningitis itself will be discussed. The subject will be discussed under four headings:

1. Osteomyelitis of the superior maxilla
2. Ocular and orbital complications
3. Osteomyelitis of the skull
4. Meningitis

Osteomyelitis of the Superior Maxilla

Osteomyelitis of the superior maxilla in infants and little children may be either acute or chronic, but the form that is of more interest to the pediatrician is acute osteomyelitis of the superior maxilla which is seen more often in infants.

Etiology.—Osteomyelitis of the superior maxilla is quite unusual in the adult and is seen very much more often in infants than in small children.

1. Trauma at birth
   a. Usually from forceps
2. Injury from cleansing the mouth in infants
3. Infected nipples
4. Infection extending from the antrum itself
   a. Not impossible at all for the antrum to act as a focus of infection in children of any age

5. Infection extending from diseased tooth buds

6. Infection of the superior maxilla—may be a part of a general infection or may be associated with osteomyelitis of other parts of the body

Symptoms and Course.—There are usually redness, swelling, and tenderness of the cheek. It is not unusual to see swelling of the eye quite similar to that of orbital complications from ruptured ethmoids or frontal. Swelling and redness of the alveolar region, canine fossa, and hard palate are usually seen. There may be a purulent discharge from the nose. This discharge may come from the antrum or from a rupture of the osteomyelitic field into the floor of the nose. It is not unusual to see unerupted teeth protruding through the swollen mucous membrane of the alveolar region.

The time of the rupture of the swollen, reddened area is quite variable, depending upon the type of infection, and the location of this rupture may be either on the hard palate, canine fossa, or floor of the nose or externally on the cheek. Through the spontaneous or operative fistula, necrotic bone can be seen or palpated. Sequestra may be present. It is not unusual to see unerupted teeth loose in the field. Of course, if the osteomyelitis does not affect the alveolar process or the hard palate but does affect the antrum and its immediate surroundings, the symptoms will be quite different. Usually after the rupture of the affected area, the symptoms, such as fever, etc., become much less marked. It seems to me, as a general thing, that osteomyelitis of the superior maxilla in little children is less virulent than osteomyelitis of the skull and that more conservative treatment can be considered.

As sequestra are formed they should be carefully removed. Good drainage is very important along with chemotherapy and supportive treatment. Some deformity is usual, and marked deformity may be present, the latter especially if the alveolar process and teeth are lost.

Case Reports.—

CASE 1.—Baby M., 1 month of age, had a history of swelling of the left side of the left alveolar process, dating practically from time of birth. The home physician incised the left alveolar process.

Examination showed markedly swollen left upper alveolar region, three teeth visibly very loose, and the left side of the nose well filled with yellow pus. The patient was given ether, the three loose teeth, which were on the surface, were removed, and an incision was made between the two posterior teeth, opening into a large cavity. In the floor of the cavity there was considerable loose bone, which was removed. The cavity proved to be the antrum and there was a fistula leading from the floor of this antrum into the floor of the nose. The patient did quite well but there was considerable drainage from the mouth as well as from the nose, and four weeks later, under ether, seven sequestra from the alveolar and antrum regions were removed. Three weeks later two more sequestra were removed from the floor of the antrum. The patient made an uneventful recovery.

CASE 2.—J. S., 7 months old, had a history of bloody discharge in the mouth and swelling of the right eye and had had a temperature of 104° F. for the previous twenty-four hours. The patient was admitted to the hospital with marked edema and swelling of the right eye. There was swelling of the right cheek, hard palate, and alveolar process. There was a fistulous tract leading from the soft tissues of the hard palate laterally to roughened bone. There was also a fistulous tract in the right alveolar process leading to an unerupted tooth.

Ether was given and the fistulous tract was enlarged, but no sequestra were found and no abscess cavities in relation to these fistulas. An incision was made in the right orbit through the conjunctival surface, and an abscess was opened which was lying between the periosteum of the floor of the orbit and the bone of

the floor of the orbit. This abscess contained about 1 dr. of pus. There was a fistulous tract leading from the floor of the orbit into the antrum and on to the anterior wall of the bone of the antrum. Drainage tubes were inserted, and the baby made an uneventful recovery without the loss of any part of the bone or teeth. It seems to me this is an example of a comparatively early operative procedure on a badly infected superior maxilla which would have resulted quite similarly to the previous case if operative interference had not been instituted.

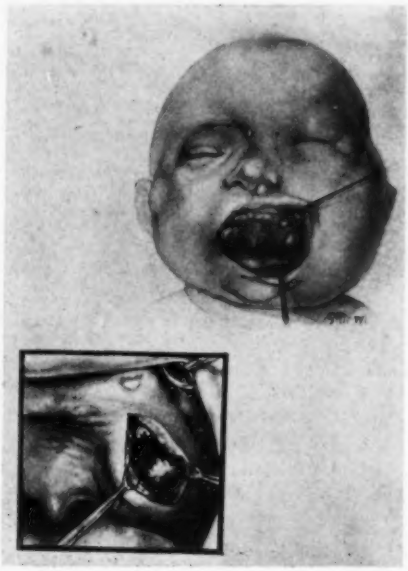

Fig. 1 (Case 1).—Osteomyelitis of upper jaw in infant.

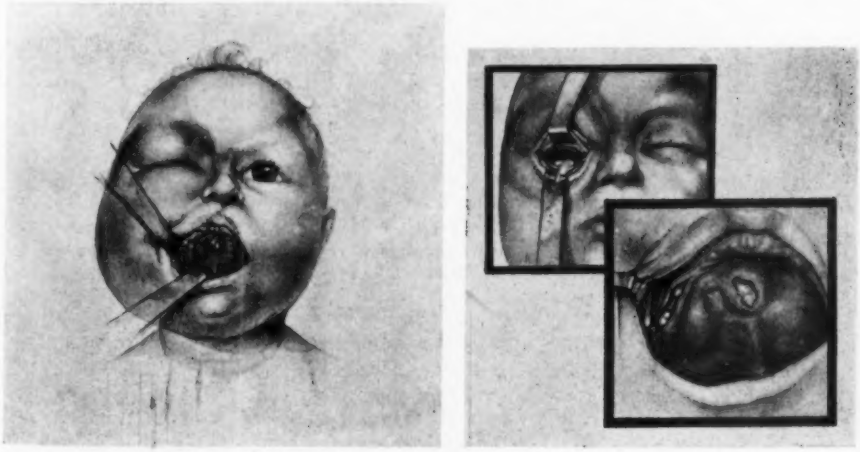

Fig. 2 (Case 2).—Osteomyelitis of upper jaw with large orbital abscess.

Ocular and Orbital Complications

Ocular and orbital complications are seen much more often than are those of osteomyelitis of the superior maxilla or even of the bones of the skull. Of course, orbital complications as a result of frontal sinus disease would be very infrequent in infants and children up to 4 years of age and quite uncommon in those 7 or 8 years old, due to the fact that the frontal is very small up to 4 or 5 years of age. Orbital complications resulting from ruptured frontal sinus infection in children of 9 years of age and older are not very uncommon. The usual orbital or ocular complications resulting from sinus disease in little children usually are due to disease of the ethmoids. Sphenoid infection should not be forgotten as a source of this affection, as it is well known that the sphenoid is quite a sizeable cavity at 4 or 5 years of age.

The usual symptoms are swelling and redness of the lacrimal sac region as well as the lids of the eye, which varies from a very slight edema to very marked swelling with proptosis and poor motility of the eye. The infection usually spreads by direct extension through the bone or through a dehiscence in the bone or by thrombophlebitis. Moderate swelling and redness of the lids for from two to four days are rather uncommon. There is usually a history of a cold with a purulent discharge from the nose, but this latter symptom may not have been noticed.

Usually if the treatment is satisfactory, nothing more than a mild periostitis will result, while if the intranasal treatment has been neglected or has been unsatisfactory, a subperiosteal abscess may result and, occasionally, abscess formation of the soft tissues around the eye, or optic neuritis, ocular complications as iritis, panophthalmitis, etc. As a usual thing, if the infection has been under the care of a well-trained rhinologist, these latter complications should not arise.

In the early cases only intranasal applications, chemotherapy, etc., are indicated, but in cases of edema and redness of the eye or lacrimal sac region, resulting from ethmoid or sphenoid infection lasting as long as forty-eight hours, which has not subsided under chemotherapy and intranasal treatment, there should be external drainage of the sinuses. I mention intranasal surgery only to condemn it. It is not only unsatisfactory but very dangerous. The external drainage of the ethmoids puts a stop almost immediately to the extension of the infection and brings to an end a very dangerous complication.

An incision through the skin over the anterior ethmoid region well below the brow is made, opening the periosteum and retracting it laterally; with a small gouge the ethmoids are opened and, if the frontal sinus is present, it can be opened through the same incision and through the same opening in the bone. A small drainage tube is placed through the ethmoid into the nose. If the abscess has ruptured through the periosteum into the soft tissues around the eye to the formation of an abscess, opening of this region with proper drainage is indicated. This latter procedure is very seldom seen, especially if the infection is followed from its incipience. Healing rapidly takes place. The drainage tube can usually be removed in two or three days, and in about seven to ten days the external wound is healed without sutures. The final result is a very slight scar, which is practically imperceptible, on the side of the nose.

Osteomyelitis of the Skull

Osteomyelitis of the skull resulting from sinus disease in children is rather uncommon, especially in infants and small children, but it is not at all uncommon in children of school age and is often seen in children from 10 to 15 years of age, especially in boys, as it is a well-known fact that swimming is one of the main etiologic factors. As M. Taylor has said, "The human being was never intended to live as fish."

Osteomyelitis of the skull usually results from infection in the frontal sinus but may originate in the antrum or ethmoid and occasionally in the sphenoid. Practically all cases of osteomyelitis of the skull result from acute sinus infection. I have never seen an osteomyelitis of the skull in a child following an operation of any kind.

Infectious diseases such as scarlet fever, measles, influenza, and the common cold are the usual precursors of osteomyelitis of the skull. Any of the pathologic factors may be encountered, but the usual ones are the staphylococcus and the streptococcus.

As to pathology, it has been divided at times into localized and into spreading fulminating forms. Some authors describe the localizing type as benign and the spreading type as malignant with a bad prognosis. To me, there as really no dividing line between the two. The localizing type may develop into the spreading fulminating type, while the spreading fulminating type with the correct treatment may have a very good prognosis.

The extension of the infection from the sinus to the bones of the skull usually takes place by a direct extension of a thrombophlebitis of the veins of the mucous membrane of the frontal to the veins of the bones of the skull.

Symptoms and Course.—Osteomyelitis of the skull may result from infection of any of the sinuses, but the usual case arises from infections in the frontal. There is usually a history of a rather severe infection in the frontal sinus with more than the usual amount of pain and tenderness and unsatisfactory intranasal drainage.

One should not forget previous operations, the history of swimming, and infectious diseases and their relation to the nasal symptoms. The first symptoms to be noticed may be swelling of the frontal region and closure of the eye associated with the sinus pain, etc., which may indicate only a periostitis or rupture of the frontal or ethmoid, but these symptoms may also indicate a beginning extensive osteomyelitis of the skull. The temperature varies from normal to 103 or 105° F., depending upon the acuteness and extent of the condition. It is not unusual to have an extensive osteomyelitis of the skull with no history whatsoever of high temperature and marked frontal sinus symptoms, but in practically all patients there is a history of sinus infection, and the examination of the nose will almost invariably show an acute or subacute infection in the frontal or other sinuses. At times the sinus symptoms are so mild and the infection has become so quiet that the sinusitis is overlooked.

In practically all cases of osteomyelitis of the frontal region there is a puffy swelling which is very indicative of this condition and should not be overlooked. Mosher has noted the importance of this edema of the soft tissues and emphasizes the fact that this puffy edema usually extends from one and one-half to two inches more peripherally than the x-ray findings and that this edema is a good guide to the limit of the infection in the bone marrow. The x-ray will always show increased density of the sinus, but the x-ray of the frontal region will not be positive, as this decreased density showing absorption or destruction of the bone will only be present after bone necrosis has taken place.

Some cases last only a few weeks, while others extend over a period of several months. Some patients have active symptoms through the entire course, while others have periods of quiescence, especially between operative procedures. At times the quiescent period may cause one to think the condition has healed, while at a later date symptoms of further extension arise. During the entire course of the disease the patient may never appear to be very sick and may recover in a few weeks, while another patient, who may be critically ill from the beginning to the end of the disease also will recover but may have one or all of the complications. Of course, the symptoms will vary greatly between the two conditions. The tem-

perature may be practically normal with very few general symptoms, while in the acute fulminating type the temperature will be high and the patient will be toxic. Redness of the skin simulating erysipelas and abscesses of the soft tissues of the frontal region are not very uncommon. Rigors are not unusual. Of course, the general symptoms would be altered by the presence of complications such as the subperiosteal abscess, abscess of the soft tissues of the frontal region, epidural abscess, subdural abscess, abscess of the brain, and meningitis and will not be further discussed.

Treatment.—

Prophylactic

a. Prevention of sinusitis

b. Treatment of sinusitis to prevent osteomyelitis

One of the more important steps in the prevention of sinusitis is probably, as Taylor said, "The control of the swimmers and the pool." Diving is always detrimental to the nasal passages. Long periods of swimming with chilling of the body should be discouraged. Correction of nasal deformities and the removal of growths, such as adenoids and tonsils, should not be overlooked. Proper treatment of infection of the nose during acute infectious diseases should be emphasized.

I shall not attempt in this paper to give the different treatments that may be carried out after sinusitis has already developed, but I do want to emphasize the importance of treatment, especially of the chronic cases in which operative procedures are necessary. These procedures should be carried out only in quiescent periods and, if there is an acute attack of sinusitis, no operating except drainage should be done. To me, any intranasal sinus surgery except drainage in acute infections in these cavities would be a very dangerous procedure. But to sit quietly by in an acute fulminating sinus infection, especially of the frontal, and allow it to rupture, with or without complications such as meningitis or osteomyelitis of the skull, is not treatment of which one could be proud.

In middle ear suppurations with moderate pneumatization of the mastoid, with marked pain in the ear and head, considerable loss of hearing, swelling of the posterior and superior canal wall, the otologist does not usually wait until there is a subperiosteal abscess, meningitis, or sinus thrombosis before drainage of the mastoid is suggested, and I doubt whether there is very much more reason for a continued period of waiting in the frontal sinus infection than there is in the mastoid. To me, drainage of the ethmoid in little children should not be an operation of last resort; but if there is marked increased density of the frontal sinus with a history of suppuration, marked tenderness of the frontal, unsatisfactory intranasal drainage, all signs which indicate unsatisfactory progress, then an extranasal drainage through the floor of the frontal or ethmoid should be carried out. Certainly if there is external swelling, closure of the eye, with the signs as described above, immediate external opening of these sinuses is indicated. The intranasal procedure with these signs and symptoms would be dangerous and would be courting complications such as meningitis, osteomyelitis, etc. If the external procedure is carefully carried out with only drainage being instituted, there is practically no danger of further extension of the disease.

The procedure which has become somewhat routine is as follows: A curved incision is made well below the eyebrow. This incision need not be more than from one-half to three-fourths of an inch long and should extend through the periosteum. The periosteum is elevated laterally from the line of incision, uncovering the floor of the frontal and the anterior ethmoids; then, with an Alexander gouge, an opening is made into the floor of the frontal and anterior ethmoids and enlarged with biting forceps. In this manner the frontal and anterior ethmoids are both opened, and drainage is carefully carried out by means of insertion of a

small rubber tube into the frontal and one between the middle turbinate and the lateral wall of the nose through the ethmoid. The mucous membrane of the frontal is not disturbed. No curettement of any kind is done. In this manner the frontals and ethmoids are drained. If there is no frontal or if the frontal is not to be opened, then only one rubber tube is inserted and that through the ethmoid. No further operative procedures are carried out at this time. These drainage tubes can be left in the wound from two to five days, depending on the course of the sinusitis. The wound is allowed to close, no sutures being necessary.

The above procedures have been very satisfactory and have given no complications. I have not seen a single case of osteomyelitis of the skull develop after this procedure. The complete ethmo-spheno-frontal operation in these acute cases should never be done, no matter how much pathology is present. If the complete ethmo-spheno-frontal operation is indicated, it should be carried out only after the condition has become quiet, usually after an interval of several months.

I shall not discuss in detail the treatment of osteomyelitis, as each surgeon must decide the best procedure to be instituted in each case. To me, whether one uses the median line or coronal incision is of little moment, because I believe this decision must be left to the surgeon in each case. It seems to me the crux of the situation is the entire removal of all diseased bone without traumatism to the surrounding tissues and the proper handling of any complications which may have arisen. To be sure that all diseased bone has been eradicated, one should remove all bone, from one and one-half to two inches farther than the necrotic area, which is visible to the naked eye. At the time of the operative procedure on the osteomyelitic focus, the removal of the floor of both frontals with the exenteration of the entire mucous membrane of these cavities may be carried out, or if the condition is quite acute and the patient is quite sick, the exenteration of the sinuses can be done one to two weeks later but should be done while the wound of the frontal is open, facilitating very much the exenteration of all mucous membrane from all parts of the frontal. This procedure usually prevents subsequent infections in the frontal sinus with its extension to the bones of the skull.

Meningitis

Meningitis resulting from sinus disease in children is not very uncommon, but the sinus disease is often overlooked as the source of the infection. A carefully taken history and good x-ray films should not be overlooked. If a diseased sinus is the focus of the infection in meningitis, beside chemotherapy and general treatment, immediate and thorough drainage of the affected sinus is indicated.

Symptoms, Diagnosis, and Treatment

O. E. Van Alyea, Chicago

Sinus disease in children is far more prevalent than is generally supposed by both the laity and the medical profession. This is due largely to the tendency on the part of physicians to disregard or overlook symptoms which might lead to a diagnosis and their tendency to neglect or minimize the importance of the disease once it is recognized.

Infections of the sinuses appear in children in all stages of their development and has been observed in the newborn infant. Benner[1] found evidence of infection of the respiratory tract, ears, and sinuses in a large percentage of stillborn infants and those who died under 2 days of age. The cause was thought to be due to aspiration of amniotic fluid following early rupture of the membranes. The sinuses at this age, aside from the antrum, may scarcely be considered more than

rudimentary cells, although being lined with mucous membrane continuous with that of the nasal cavities, they are subject to any infections which may involve the nose.

Ebbs[2] found that in a group of 495 children under 14 years of age who died of a variety of conditions, a purulent infection in one or more of the sinuses was present in 30 per cent.

Schoenberg,[3] in a similar study, found on autopsy empyema of one or several sinuses in 154 of 232 children, or 66.4 per cent.

Children are fully as susceptible to nasal infections as are adults. The inception of the infection is enhanced in children by the prevalence of exanthematous disease, the comparative large size of the sinus openings, and impaired ventilation due to mouth breathing. Other etiologic factors often mentioned are avitaminosis, allergy, hypothyroidism, and poor hygiene. Sinusitis following swimming is often of a severe fulminative nature. This is due to the sudden introduction of virulent organisms into a normal sinus which has not had the advantage of establishing any local barriers to the infectious process.

Cone[4] recently emphasized the psychologic and psychiatric factors which influence changes in the mechanism of vasomotor control. He feels that the child suffering from sinus disease is usually of the nervous type and possessed with anxious parents.

Symptoms.—The symptoms of sinus disease in children are similar to those in the adult. In some cases the constitutional effects may be more pronounced because the infection tends to be more rapidly absorbed by the "virgin territory" of the sinus mucosa.

Characteristic of sinus disease in children are frequent colds or a long-standing single nasal infection, nasal blockage, and discharge, pharyngeal bands, and the presence of lymphatic nodules in the pharynx and nasopharynx. The child may have a poor appetite, be underweight, have headaches, and may be subject to attacks of otitis media, sore throat, and cough.

Diagnosis.—The disease is often easily recognized by characteristic symptoms, anterior rhinoscopy, transillumination, x-ray, and sinus lavage. There are, however, many children in whom the diagnosis is difficult and the condition may exist unrecognized and untreated for years. Attention may be directed to other areas for the cause of the symptoms. In many instances tonsils and adenoids or the lungs have been thought to be the cause of the frequent colds, sore throat, cough, and other symptoms, yet no improvement follows treatment of the chest and removal of the tonsils and adenoids. A pronounced case of mistaken diagnosis was reported by Bilchick[5] in a nine-year-old child admitted to the hospital with an acute suppurative otitis media. A simple mastoidectomy was performed, apparently being justified, yet revealed no pathology. The child died the following day and autopsy revealed an acute left pansinusitis which involved the sphenoid and which had extended to cause a cavernous sinus thrombosis. The sinuses had been only hazy on roentgen examination and there had been no pus in the nose. This case illustrates the importance of including a verticomental view with the other roentgenograms of the sinuses. This view is taken with the patient prone and the extended chin on the film. It delineates clearly the sphenoid cavities and reveals the presence or absence of purulent material.

Examination of the Pharynx: Study of the oro- and nasopharynx may furnish valuable clues toward the recognition of a sinus infection. The presence of a purulent exudate in the epipharynx alone is almost proof positive of sinus disease. The possibility of a foreign body in the nose should naturally be ruled out before the diagnosis of sinusitis is made. Lymphoid nodules in the oro- or nasopharynx and redness of the lateral bands should call for a thorough study of the sinuses. As Crowe[6] states, lymphoid tissue is an integral part of the mucous membrane of

this area and its recurrence after removal is to be expected. This is an important observation, yet the recurrence of adenoid tissue after repeated operations may be a strong indication of an infection in one of the nasal sinuses.

General Management.—In the acute nasal and sinus infections the treatment in children is similar to that in adults. Acute attacks tend to heal spontaneously and those cases which persist do so because of drainage impairment. All writers are agreed that patients do better when put to bed in a warm, well-moistened room and that simple common sense treatment hastens recovery and prevents complications. Energetic local treatment is avoided, yet measures to aid in the comfort of the patient are introduced early and maintained throughout the course of the disease. Codeine and other drugs are used along with heat for the relief of pain, and vasoconstrictors are instilled into the nose to enlarge the breathing space and promote drainage. Heavy secretions should be drawn from the nose by suction. A simple medicine dropper often suffices for this purpose.

Intranasal Medication.—Intranasal medication in all forms of nasal and sinus disease is undergoing constant change at the present time. This is due to our ever increasing knowledge of nasal physiology and the histopathology of the sinus mucous membrane.

Considerable investigative work during the past fifteen years on the ciliated mucosa, the highly vascular submucosal stroma, and the chemical characteristics of the nasal secretions has brought about an entirely new viewpoint concerning nasal medication. We know now that solutions used in the nose should be non-detrimental to ciliary activity, should be isotonic, and should have a pH slightly on the acid side.

To conform to these requirements eliminates, to a large extent, many of the preparations which have enjoyed a wide usage in the past. Included in this list are solutions of mild silver protein and those containing oil. A common practice of the past has been instillation of mild silver protein into a child's nose with the patient flat on his back. There are several reasons why this form of therapy should be discontinued, the least of which is that it is absolutely worthless and, perhaps, the greatest is that it is dangerous.

Other preparations to be avoided during an acute upper respiratory infection are those containing atropine which causes drying and cessation of ciliary action and inhalants of benzedrine which elevate the pH of the nasal secretions to an unhealthy state.

An effective combination now in common use which complies with all the requirements is ephedrine, 1 per cent, in normal physiologic salt solution. Some of the synthetic preparations may be substituted for ephedrine and Ringer's or Locke's solution for the normal saline. This solution is an effective vasoconstrictor and may be used on children of all ages. The best means of application is instillation with the patient in the head low position of Proetz or Parkinson. Young children may be held on the nurse's or mother's lap and older children, as a rule, willingly assume the position on a couch or bed. A dropperful of the solution is instilled into each nostril and kept there for from thirty to sixty seconds. The head is then faced downward and the solution allowed to run out. This form of treatment affords relief for two or three hours, and, being harmless, may be used at intervals if the comfort of the patient warrants it. Suction is not used in this stage, being reserved for the persistent cases.

Adjunct Therapeutic Measures.—

Thermotherapy: Heat applied to the face in the form of infrared rays or short wave diathermy is helpful in acute sinusitis for the relief of pain and in combating the disease. Shea[7] advocates also hot moist packs and these may be

alternated with the infrared lamp. Roentgen thearpy is recommended by Hodges[8] in the later stages of sinus disease in children, and it was also used by Youngs,[9] who noted no harmful effects. Its value, however, is questionable.

Foreign protein injections are thought by many to be helpful in the acute stage, and vitamin C in large doses is also recommended. Ascorbic acid, 200 or 300 mg., is given in water or orange juice daily. The adult dose is 1,000 mg.

The Persisting and Recurring Cases.—In the long-standing acute cases, the subacute, the chronic, and the recurring types, measures are introduced to promote drainage of infected cavities, and, while so doing, to attempt to establish immunity in the patient, and to lessen the frequency of acute attacks.

The question of climate is always brought up whenever the management of sinus disease is considered. Children undoubtedly do better in a warm, dry climate and many apparently are not free from their upper respiratory infection if exposed to a cold, northern winter, yet many still have their sinus infection after a winter in Arizona or Florida or California. Most children, if properly treated, may exist as normal individuals in the North as well as in the South.

Vaccine: Shea advocates the use of a vaccine made from the child's nasal discharge during his first cold of the winter, improved with the addition of cultures from the intercurrent infection prevalent at the time. Walsh attempts to increase local immunity by spraying the vaccine daily into the nose.

Vitamins: Spiesman[10] thought large doses of vitamins A and D lessened the severity and the number of attacks when taken over a considerable period of time.

Tonsils and Adenoids: Griffiths[11] found in a large series of patients that sinusitis was more common in children whose tonsils had been removed than in the others. Crooks[12] cited twenty-four cases in patients in whom the tonsils and adenoids were removed because of the presence of mucopus in the antrums. Six months after the operation the infection was still present in sixteen.

The removal of tonsils in the hope that in so doing the sinus disease may be cleared up is a mistake, yet adenoids, if they block the passage of air through the nose, should be removed. Improvement in nasal breathing aids the sinuses in the evacuation of secretions by the alternating plus and minus changes of the air pressure within the cavities produced by expiration and inspiration.

Intranasal Procedures.—After the stage of acute edema has passed, local therapeutic measures available are displacement therapy, infracture of the middle turbinate, and sinus lavage.

In many patients disturbance of drainage of the sinuses in the anterior group is due to a blocked middle meatus, and adequate drainage space may be attained by pushing the turbinate toward the septum. This is a simple office procedure and may be carried out in the older children under local anesthesia.

Displacement therapy is most effective in the lingering cases of two or three weeks' duration. The acute edema has subsided yet infection persists. The child is placed in the head low position and several cubic centimeters of 25 per cent ephedrine saline solution are instilled into the nares of the involved side. Mild suction is alternately induced then released a few times. The shrinking action of the solution enlarges the openings of the sinuses it contacts and the solution passes into the cavity displacing the accumulated secretions. Should the infection be located in the anterior ethmoid cells, immediate improvement is noted; a similar result may be gained in the other sinuses, especially those which drain into the middle meatus. The displacement treatment may be repeated once or twice a week until the symptoms disappear.

In some patients this treatment fails because of a sealed middle meatus or closed ostium. In many patients, however, displacement treatment may be the means of clearing up chronic cases which have existed for months or even years.

In the event that the antrum is involved and other methods fail, irrigation is indicated. If necessary, the child is put to sleep, but in many instances the natural opening may be reached under local anesthesia if great care and tact are used. Often one treatment provides the impetus which promotes a healing process. If many irrigations are required, a small window may be placed in the inferior meatus to be used for that purpose. If irrigation therapy fails completely, permanent windows are made which, in uncomplicated cases, are effective in 97 per cent of patients.

The frontal and sphenoid sinuses, though less likely to be involved than the ethmoid and maxillary, may also be irrigated. The natural openings of each sinus is accessible in 85 per cent of patients. Removal of purulent material by lavage at the proper time by a simple measure may be the means of successfully terminating a case which otherwise might remain chronic with a suppurating cavity and later require extensive surgical procedures.

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The Relationship of Allergy to Sinus Disease in Children

French K. Hansel, St. Louis

Among the diseases of the nose and paranasal sinuses in children, the most common conditions encountered are (1) the common cold, (2) acute, subacute, and chronic sinusitis, (3) allergy, and (4) allergy complicated by infection. The diagnostic problem, therefore, is the differentiation between allergy and some type of infection. The acute and subacute infections, characterized by a sudden onset with fever, sore throat, cough, profuse nasal discharge which is first watery, then mucopurulent, are not difficult to recognize. In the absence of fever and sore throat, infection must be differentiated from an acute exacerbation of allergy. Repeated recurring exacerbations are more commonly of allergic origin. During the spring and summer months, trees, grass, and ragweed hay fever must be considered.

Among the chronic nasal and sinus conditions, allergy, in our experience, has been found more commonly than infection. In children, chronic sinus allergy is

not frequently complicated by infection. Marked edematous changes and polyposis are rare before the age of puberty.

In the cases of nasal allergy, sneezing and itching of the nose are common symptoms. In the chronic infections these symptoms are almost always absent. Although pallor of the mucosa is usually observed in allergy, varying degrees of redness is not infrequent.

In the x-ray examination of the sinuses, varying degrees of cloudiness, especially in the antrums and ethmoids, may be noted in allergy or in infection. This diagnostic procedure has, therefore, its limitations.

In the differentiation between allergy and infection the most definite and reliable diagnostic procedure is the microscopic examination of the nasal and sinus secretions. The gross appearance of secretion is often misleading and should not be relied upon. Thin watery, thick opaque or yellowish secretion may be noted in either condition and yet the cytologic pictures may be entirely different. The consideration of the microscopic examination from the standpoint of eosinophiles and neutrophiles, taking into consideration the relative numbers and proportions of each, presents a diagnostic picture which has definite significance.

For the relief of frequent colds and bronchitis, allergy must always be considered before advising the removal of the tonsils and adenoids. Bronchitis is often a forerunner of asthma in children; therefore, allergy and infection must be differentiated.

Pediatric Complications Referable to Sinusitis

E. J. Huenekens, Minneapolis

My assignment is to represent the pediatric viewpoint in relation to sinusitis, and this largely resolves itself into a discussion of focal infection. At the outset I wish to make it clear that it is very difficult to distinguish between the roles played by the tonsils, adenoids, and the sinuses in focal infection. They should be regarded as definitely interrelated, and the sinuses usually come to the foreground only when the tonsils and adenoids have been removed. The question of focal infection is a very controversial one, and the medical world can roughly be divided pro and con. Because in the past far too many tonsils were removed, and frequently for the wrong reasons, there has been a tendency to ridicule the whole idea of focal infection instead of battling against the excesses done in its name. A calm unemotional approach to this question is in order.

In childhood, for all practical purposes, possible foci of infection consist of the tonsils, adenoids, and nasal accessory sinuses, especially the maxillary sinuses. I cannot emphasize too strongly that the removal of foci of infection must be decided in every case as an individual problem on the basis of a complete history, the local condition of the nose and throat, and a thorough general physical examination. If this be granted, I firmly believe that the general practitioner, the internist, and the pediatrician are frequently in a better position to decide on the advisability of removing sources of infection than the rhinologist, who tends to make his decision on the basis of local pathology. To quote Dean, "Practically, the removal of tonsils is always a gamble. Even if they are infected it is not necessarily true that they are the focus for systemic disease." The severity of the diseased condition one is seeking to remedy and the lack of other therapeutic approaches play a large part in deciding for or against the eradication of foci of infection. Even though complete assurance of cure cannot be promised, it may be sound clinical judgment and a good gamble to remove the sources of infection. If tonsillectomy fails to remedy the diseased condition, the sinuses should be considered as another possible focus of infection.

One of the greatest problems in pediatrics is what to do for children who suffer from frequent upper respiratory infections. Ultraviolet light and various vitamins

and vaccines have been tried with slight success. Until better prophylactic agents can be found, removal of foci of infection offers the best chance of cutting down the incidence of these infections. The decision should be made not only on the frequency, of the infections, but on their severity and their effect on the general body health. I have frequently noticed that after tonsillectomy upper respiratory infection may be lessened but still persists in altered form, as, for example, a more or less chronic cough. In such instances the treatment of sinuses is often of inestimable value.

The relation of sinusitis to systemic disease is no more clear-cut than in otitis media. Drainage of the maxillary sinuses is the operation of choice for recurring otitis media and even for subacute and chronic otitis media. It has been a surprise to me how frequently drainage of sinuses has relieved a more or less chronic otitis media and made a mastoid operation unnecessary. If there is no emergency involved, I always insist on a sinus drainage before a mastoidectomy is permitted. From personal experience over a period of years I recommend this procedure very highly, even though it has received little consideration in medical literature. Even if mastoidectomy is necessary after sinus drainage, the removal of foci of infection will help prevent further mastoid disease, which is quite possible after a mastoidectomy.

The relation of foci of infection to the rheumatic syndrome has been an important controversy for years. Infections of the nose and throat are probably not the true cause of rheumatism but are frequently the immediate exciting cause. When such is the case, the tonsils and adenoids should be removed and, if this brings no relief, sinus drainage should seriously be considered. Kaiser, of Rochester, has written many papers to show that tonsillectomy does not prevent rheumatism and probably does little to alleviate it after it has begun. I accept his work as sound but feel that only part of the problem has been attacked because the sinuses have been completely ignored. In Kaiser's work, and in similar statistical studies, the answers are all recorded as definite success or failure. In my experience removal of foci of infection markedly alleviates the rheumatic condition. But in a statistical study such cases are recorded as failures if even mild rheumatic attacks recur. The relation of infection to rheumatism is nowhere more completely demonstrated than in the successful prophylactic use of sulphanilamide in these cases. It would therefore seem logical to supplement such prophylactic therapy by the removal of foci of infection. This is another important field where the sinuses have been largely overlooked as a source of infection.

In recurring bronchitis, chronic bronchitis, and bronchiectasis the sinuses are an important source of infection. It is especially in these cases that allergy must be ruled out, and this is not an easy thing to do. The seriousness of chronic bronchitis and early bronchiectasis is so great that the patient usually should be given the benefit of any doubt and the tonsils and adenoids removed, but, even more important, the maxillary sinuses should be drained.

Acute glomerular nephritis in childhood is practically always secondary to an acute infection elsewhere. Fortunately the prognosis is usually good, but in most patients it is sound practice to remove the tonsils and adenoids and, if indicated, drain the sinuses after the disease has subsided to prevent recurrence. Occasionally, where convalescence is unduly prolonged, focal infection removal might be indicated while the disease is still active.

Sinus disease must be considered as a possible factor in such diverse conditions as certain types of pyuria which recur only in connection with upper respiratory infection; convulsions with each recurring bout of fever; abdominal pain which simulates appendicitis but which on careful observation can be shown to be due to upper respiratory infection; and asthma where infection is the exciting cause.

In conclusion, the treatment of sinus disease does not always involve an operation. Certainly in the milder types many can be cared for in the office of the

pediatrician by shrinking of the nasal mucous membrane and then applying moderate suction from an electric- or water-powered apparatus. Operative procedures are often obviated. A very widespread prejudice among physicians and the laity against sinus drainage is quite unfounded as regards children. One reason for this is the little-known fact that in infants and young children the floor of the antrum is much higher than in adults, so that in endonasal drainage operations we get better drainage than in adults becase it is dependent drainage. I have had many patients who have not benefited by sinus treatment, but I have yet to find one who has been definitely harmed.

Chest Findings in Sinusitis in Children

Paul Holinger, Chicago

The association of bronchopulmonary disease with sinusitis in patients of any age is an established one. However, in children we may study its pathogenesis and from these observations may question certain heretofore well-accepted facts in an effort to clarify principles of therapy.

Anatomically there are three routes by which infection may travel from the sinuses to the dependent bronchi: by a continuity of the mucous membrane surfaces, by gravity through the pharynx, larynx, and trachea, and by way of the mediastinal lymphatics. It should be mentioned here that the first two routes are definitely and easily reversible and that some experimental work has demonstrated that the third route may likewise carry infection from the chest to the sinuses as well as in the more accepted direction—from the sinuses to the chest.

Bronchopulmonary involvement in sinus disease may be divided into distinct clinical entities:

1. Chronic Cough With Chronic Sinusitis.—Probably the most frequent symptom referable to this discussion is the "postnasal drip" with its accompanying cough. Locating the sinuses involved in such a patient is a difficult task. However, the chest findings may easily be described. The physical findings show scattered râles at the bases of the lungs, and bronchoscopy generally shows a definite bronchitis with frothy mucopus present, but unless the condition has persisted a long time, there is generally no actual bronchiectasis. Children with such conditions improve rapidly with active sinus therapy, postural drainage, occasional bronchoscopic aspiration, and the administration of autogenous vaccines. Cough sedatives are absolutely contra-indicated in such children as they tend to aid in retaining infected secretions.

2. Nasal Allergy and Asthma.—This subject was discussed comprehensively by Dr. Hansel and need be only briefly mentioned here. It may be illustrated by citing the case of a child with asthma and many nasal polypi. The child had an asthmatic chest, with many râles throughout and with recurring attacks of asthmatic bronchitis and bronchopneumonia. The chest x-ray showed diffuse peribronchial infiltration and patchy areas of atelectasis. Pediatrics, allergic, rhinologic, and bronchoscopic management in cooperation with each other are essential for the best management of such a patient.

3. Sinusitis and Bronchiectasis.—Recent surveys of this problem in the literature suggest that sinusitis is not an important etiologic factor in most cases of bronchiectasis in children. In our own series of 121 cases of bronchiectasis, all the children were carefully examined in the department of otolaryngology, and in only eighteen was sinus pathology suspected and proved by x-ray. To emphasize this point further, it should be mentioned that most of the eighteen children with sinusitis had had bronchiectasis over a period of several years and that from their records it appeared that their pulmonary pathology had preceded their sinus pathology. Acute atelectasis associated with upper respiratory infections, which

increasing evidence suggests as the commonest etiologic factor of bronchiectasis in children, was the usual history of onset in our bronchiectatic patients.

While minimizing sinusitis as a causative factor in bronchiectasis, it must be stressed that patients with bronchiectasis who have demonstrable sinus pathology will receive direct improvement of the pulmonary symptoms if the sinuses are cleared of their infection. Without such therapy, treatment directed toward the pulmonary infection would be of little value.

Sulfonamide Therapy of Nasal Sinusitis

George S. Livingston, Chicago

Sulfonamides have taken their place in the treatment of nasal infections as they have in the treatment of most of the other acute infections. A consideration of their effectiveness is important but is sometimes difficult to evaluate. Since acute sinusitis is usually a self-limited disease, tending toward spontaneous resolution, any therapeutic measures are likely to appear valuable but may be only incidental to the natural course of the disease. When, however, drugs such as the sulfonamides have demonstrated their curative powers in such highly fatal diseases as meningitis, a solid pharmacologic basis has been established which warrants their use in less severe infections. Bearing in mind, however, the possibilities of sensitization and toxicity, it becomes a matter for careful consideration before a decision is made whether or not to use these drugs in any individual case.

Statistical studies do not lend themselves well to the study of simple self-limited infections. Close observation of individual cases, however, will give the clinician a good opportunity to make a fairly accurate appraisal. Having seen a large number of patients with uncomplicated acute sinusitis make progressive improvement over a period of from one to two weeks without sulfonamides, he will be quick to note the rapid, even critical improvement occurring in two or three days with sulfonamides. While this experience is not universal, it occurs with sufficient frequency to demonstrate the usual efficacy of sulfonamide therapy. If prompt improvement does not occur with proper administration of the drugs, one may assume either ineffectiveness or an exceptionally severe infection. In the latter event, the persistence of administration may be the determining factor in preventing complications. It seems quite likely also, that sulfonamides may prevent many cases of sinusitis when given early in the course of acute upper respiratory infections. Many observers have reported on the marked decrease in the incidence of acute mastoiditis because of the early administration of sulfonamides in otitis media. An analogous situation occurs in the relationship between acute sinusitis and the common cold. The experience of Siegel[1] is noteworthy. In 109 cases of acute upper respiratory infections in children, he gave sulfadiazine to fifty-four and withheld it from fifty-five. Those in the treated group responded promptly in from twenty-four to forty-eight hours with a drop in temperature, lowered toxicity, and rapid recovery. In those in the control group the course was variable and unpredictable. Some recovered rapidly, while many others did not.

Although sulfonamides have proved their value, they should not be relied upon solely in the treatment of acute sinusitis. The usual indications for other necessary measures should be heeded as they arise and applied as needed. The administration of sulfonamides by mouth in the treatment of acute sinusitis is governed by the same factors as in the treatment of other acute infections. The objective is to bring an adequate amount of the drug through the blood stream to the site of infection, to maintain the required concentration continuously until recovery has taken place, and to choose the drug most likely to act effectively against the particular organism that is causing the infection. The majority of acute sinus infections are caused by hemolytic streptococci, pneumococci, and staphylococci. While sulfanilamide is effective against streptococci and sulfapyridine, against pneumo-

cocci, neither is active against staphylococci. Furthermore, it may not be feasible, in many instances, to determine the bacterial offender. Sulfathiazole and sulfadiazine which are effective against all three organisms, and some others as well, are likely to prove much more reliable in most cases. Sulfadiazine seems at present to be the drug of choice. It has a lower toxicity than sulfathiazole, is excreted more slowly, thus facilitating the maintenance of adequate blood levels, and passes more readily into the cerebrospinal fluid. This last is an important consideration if an intracranial complication is impending or present. The amount of acetylation is lower, so that urolith formation is less likely than with sulfathiazole.

The usual dosage is 1 gr. per pound of body weight in twenty-four hours, divided in six doses given at four-hour intervals. In severe and fulminating infections, especially with sepsis or meningitis, 2 gr. per pound may be given at first, and in such instances it is well to give the total twenty-four-hour requirement as the first dose. It is advisable to determine the blood concentration of the drug after the first twenty-four hours in order to regulate subsequent dosage. From 5 to 10 mg. per 100 c.c. of blood are considered to be satisfactory levels, although the more seriously sick patients should be kept at the maximum. When definite improvement has occurred, ¾ gr. per pound, divided in four doses at six-hour intervals is usually adequate for the remainder of the course. In fulminating infections or with meningitis, treatment should be initiated by the intravenous administration of the twelve- or twenty-four-hour requirement of a 5 per cent solution of sodium sulfadiazine in sterile distilled water. This is stopped when an adequate blood level has been established and if the patient can take the drug by mouth. It is probably better to give sulfadiazine after rather than before meals. Peterson and Finland[2] have determined that it is absorbed more slowly but more completely when given after a meal than on a fasting stomach. Added alkali, such as an equal amount of sodium bicarbonate, increases the amount of drug absorbed when given after a meal. Alkali hastens absorption when given on an empty stomach but does not increase the amount absorbed. It is imperative to continue treatment until the patient has been well for several days. Too early withdrawal of the drug is likely to be followed by a relapse, which may be refractory to further medication. This is especially true if early dosage has been too low, as this tends to favor the development of a sulfonamide-fast organism.

Toxic reactions to sulfonamides are quite common, although usually not severe. Nevertheless, Lyons and Balberor[3] found that one-third of all their patients treated with sulfonamides a second time developed a sensitivity sufficient to interfere with further use. The most frequent evidences of toxicity are nausea and vomiting, often accompanied by headache. If mild, they may subside even though treatment is continued. If severe, however, the drug may have to be withdrawn. These reactions usually occur early in the course of treatment.

Sensitization, if it occurs, usually becomes manifest between nine and twelve days after the first administration of the drug. It is characterized by a chill or chilliness, followed by a sharp rise of temperature to 104° F. or higher, and is frequently accompanied by an itching cutaneous eruption. With sulfathiazole, conjunctival injection is often present. This is a warning to stop the drug, as continuance may lead to more serious complications. Upon withdrawal, the symptoms usually disappear in from two to four days. Subsequent administration is quite likely to cause a repetition of the reaction. Nelson[4] reported the case of a woman with cystitis and urethritis who was treated with sulfathiazole. The initial treatment caused no reaction. On the eighth day 5 Gm. caused a toxic reaction which stopped when the drug was withdrawn. On the twenty-second day, 4 Gm. of sulfathiazole caused a reaction. On the thirtieth day, 2 Gm. of sulfathiazole, giving a blood concentration of 3.1 mg. per 100 c.c. caused another reaction. On the thirty-eighth day, 4 Gm. of sulfadiazine, with a blood level of 3.3 mg. per 100 c.c.,

caused another reaction. On the fiftieth day, 4 Gm. of sulfapyridine, with a blood level of 5.1 mg. per 100 c.c., and on the sixty-fourth day, 10 Gm. of sulfanilamide, with a blood level of 6.6 mg. per 100 c.c., also caused reactions. Gallagher[5] has observed sensitivity to persist for two years in one patient. Wedum[6] could not demonstrate sensitization in animals with simple, uncombined sulfonamide compounds. He was, however, able to do so by the use of azoproteins. His experiments, using sulfonamides combined with egg white, human serum, and beef serum, produced sensitization, as demonstrated by skin tests, anaphylaxis, and precipitin tests. While the strongest reactions occurred with the specific sensitizing sulfonamide azoprotein, weaker crossed reactions also occurred using other members of the sulfonamide group.

Although the proportion of serious complications is not large considering the widespread use of these drugs, the literature contains many references to agranulocytosis, acute hemolytic anemia, hepatitis, hematuria, and anuria. Sulfathiazole and sulfapyridine have been known for some time to be likely to cause uroliths because of the high rate of acetylation. Sulfadiazine, with a low degree of acetylation, may, however, also cause severe renal damage. Lederer and Rosenblatt[7] reported four cases of death attributable to sulfathiazole, in which there was widespread visceral focal necrosis. Merkel and Crawford[8] also reported four such deaths. In these cases the fluid intake and urine output were adequate and the highest blood level was 10 mg. per 100 c.c. There were found many discreet areas of focal necrosis in the lungs, kidneys, liver, spleen, and bone marrow. Sulfadiazine also is not entirely without guilt in this respect. Raines[9] reported two cases of ureteral obstruction following its use. Bradford and Shaffer[10] had a case of fatal urinary suppression from sulfadiazine in which the autopsy showed acetylated crystals in the renal pelves and tubules, with adjacent ulceration, intense inflammation, and necrosis. In the case reported by Hellwig and Reed[11] the patient had taken 24 Gm. of sulfadiazine in nine days. Fatal anuria resulted. At autopsy the kidneys showed a severe degeneration of the convoluted tubules, similar to that found in mercury poisoning. These references are cited not to deter one from the properly indicated use of these valuable drugs but to sound a note of caution against their promiscuous and needless administration.

A difficult problem sometimes arises during the course of a sinus infection under sulfonamide treatment. If a patient on adequate dosage develops high fever, headache, nausea, and vomiting, the differential diagnosis lies between drug toxicity and meningitis. In the former event the drug must be promptly withdrawn, while in the latter, the dosage should probably be increased. A wrong decision in either case may place the patient in great jeopardy. If a rash and leucopenia are present, the probability of a drug reaction is great. Some drug reactions, however, are not accompanied by a rash, and in some cases there is hyperleucocytosis. In such patients a spinal puncture must be done. A further difficulty may arise, if a chill and high fever occur, in distinguishing between sulfonamide toxicity and sepsis. Here the blood culture may be helpful. The possibility of masking of symptoms by sulfonamides is present in sinusitis just as it is in otitis media but is not usually of as great importance. Nevertheless, with an eye to possible intracranial complications, masking must be kept in mind.

The local use of sulfonamides, now well established in other fields, has also proved valuable in the treatment of sinusitis. The advantages are obvious. When introduced directly into an infected sinus, a much higher and more effective concentration of the drug can be established where it is most needed than can be accomplished by oral administration. This not only insures more complete bacteriostasis but avoids toxicity, since very little absorption into the blood stream occurs. The compounds are not irritating to the nasal or sinus mucosa. Their introduction, however, is attended by some difficulties. Sulfathiazole, especially, forms

heavy clumped masses when insufflated in powder form. All of the compounds are difficult to inject in aqueous suspension because they settle out too rapidly. Recently this disadvantage has been overcome by the use of microcrystals. Chambers and his co-workers[12] report that microcrystals of sulfathiazole can be prepared by crystallization from a solution of sodium sulfathiazole at low temperature, applying violent agitation by sonic vibration. They can be easily suspended in water up to 30 per cent by weight. Clumping does not occur, and the minute size of the crystals favors more rapid solution. In this form no foreign body reaction occurs. None of the drug could be found in the tissues ten days after implantation. Silcox and Schenck[13] reported on the local application of suspensions of microcrystalline sulfanilamide and sulfathiazole in cases of acute and chronic sinusitis. They noted the ease of introduction, absence of clumping and of irritation, and negligible absorption into the blood stream. They found a 5 per cent suspension to be adequate for all purposes and obtained excellent results. This suspension can be introduced into the nose easily by spraying or dropping. There is some evidence that if so used it may shorten the course of the common cold and tend to prevent complications. In cases of acute sinusitis, displacement irrigation with the suspension is easily accomplished. It can also be introduced directly into the maxillary sinus by means of a cannula. After sinus surgery the local use of sulfathiazole is very helpful, as it favors rapid subsidence of suppuration.

Solutions of sodium sulfathiazole should not be used in the nose because of their caustic action. Futch, Rosenvold, and Stewart[14] demonstrated the destructive effect of a 5 per cent solution on the nasal mucosa of rabbits.

In cases of chronic suppurative sinusitis the oral administration of sulfonamides has not proved successful. Their local use, however, is always beneficial. One regularly notes the diminution of suppuration and odor. In those cases, however, with severely damaged membranes and osseous necrosis, a cure will not result from the use of sulfonamides alone. The proper surgical treatment must be instituted and the drug then used as an adjunct in postoperative management.

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DISCUSSION

DR. EDWARD CLAY MITCHELL, MEMPHIS.—In 1920, with Dr. John J. Shea, of Memphis, I began the study of sinus infection in children. We divided the patients in our observations in several groups:

1. Those suffering from sinus
2. A group of sinus-free infants to observe the growth
3. A group of sinus-free infants with a family history of sinus infection
4. A group of children with repeated colds who had previously had tonsils and adenoids removed

5. A group of children showing evidence of focal infection, as urinary, etc., which may be attributed to sinus infection

These children were observed at intervals by physical examinations, both otolaryngological and general, transillumination, and x-ray. Many of these patients were followed for a period of twenty years.

Our first paper was read in 1922 in New Orleans. We have read several since.

Our observations would lead us to believe the following at the present time:

1. Sinus infection, both acute and chronic, occurs in children.

2. Undoubtedly the sinus is a focus of infection for other conditions.

3. Tonsils and adenoids are often removed without result because of sinus infection.

4. The treatment of sinus infection is often hindered by bad tonsils and adenoids.

Growth.—

1. There is a regular cycle of growth which varies in different individuals but follows the same pattern.

2. This growth, or lack of growth, may affect one or all of the sinuses, or may be unilateral or bilateral.

3. Family history of sinus disease undoubtedly plays a role. The sinuses of a child have a developmental history and also a disease history closely approximating that of the parent it most resembles facially.

Sinuses Grow as a Result of Ventilation:

1. Any condition, be it infection or allergy, which prevents proper ventilation prevents growth.

2. A properly ventilated sinus grows properly and is not diseased.

3. The time to cure or even permanently improve the sinuses is by proper ventilation during period of childhood or during growth period.

Method of Treatment.—Our observations would lead us to approve of any treatment which will properly ventilate the sinuses.

In some cases, undoubtedly, washing through the natural opening and even forming a window is necessary.

DR. GEORGE J. GINANDES, NEW YORK.—I feel that not only do allergy and infection as such play a role in altering the physiology of the nose, but also that certain physical conditions such as changes in temperature, barometric pressure, and humidity exert a significant influence. Naturally, once the nose has been altered by these factors, its capacity for adjustment to such changes is impaired and reactions of varying degrees can result.

With regard to the effect of camp on nasal infections, it has always been my impression that shortly after children arrive at camp, there is a wave of upper respiratory infections. This subsides, only to return in the early and middle parts of August. I have explained this on the grounds that the first wave is due to the exchange of bacteria that is effected when groups of children from different sources come to live under the same roof.

After a short period in the sun and air, and with each other, these children develop more resistance, and the upper respiratory infections seem to diminish in number. Under the exhilarating influence of the first few weeks of camp life, the children develop a false sense of security. The athletic program becomes increasingly taxing as the weeks go on. This plus the atmospheric changes which occur in August is responsible for the second wave of infections which occurs during this time. There are of course other factors such as infections brought in by visitors at camp, etc.

I think it is particularly important that children at camp be watched against overexertion. Children with bad noses should be especially guarded against underwater swimming. Frequently a child returns from camp with an active sinusitis which has been encouraged by the camp routine.

DR. GERALD M. CLINE, BLOOMINGTON, ILL.—The increased incidence of colds and upper respiratory infections among people during the fall months, undoubtedly, is also caused by the prevalence of pollens (especially ragweed and molds) in the air at that time of the year. Mold content of the air reaches its peak in this community about the last week in July or the first of August. The alternaria mold perhaps is the big offender. Ragweed pollen which starts as early as the first week in August is very often the cause of the first symptoms of a cold among the susceptible individuals. I feel confident that this saturation period of weed and mold allergy leads to more frequent colds for these individuals throughout the winter months, at least up to around February, when some of them will seem to stabilize themselves and have fewer colds from then on.

I believe we most all agree that the age incident does not play as big a part as we formerly thought, for now I see many children and even infants 6 months and under with proved symptoms of pollenosis in one form or the other. Specific treatment and especially climatic changes during these periods have borne out these observations.

I cannot pass without speaking of the dust factor and susceptibility to animal emanations particularly among susceptible children. Raking and burning of leaves in the early winter may often touch off the trigger mechanism. Removal of animals and especially the feather pillow does more sometimes to prevent colds than all the vitamins, cold vaccines, etc., put together. The high incidence of allergy among the human race to me makes every cold susceptible a suspicious associated allergy problem until disproved.

News and Notes

1944 Annual Meeting

The Executive Committee has decided to hold an annual meeting of the Academy in 1944. The meeting will be held in St. Louis at Hotel Jefferson, Thursday to Saturday, November 9, 10, 11. These dates precede the meeting of the Southern Medical Society which will be held in St. Louis the first part of the following week. Thursday will be given over to clinics with program meetings on Friday and Saturday.

The **American Board of Pediatrics** will hold an examination at the time of the Academy meeting in St. Louis in November. The written examination will be held locally under a monitor on September 22.

Book Reviews

Tuberculosis Congenita. Mario Waissmann, Buenos Aires, 1942, El Ateneo, 170 pages.

The author reviews the birth histories of 737 tuberculous mothers delivered in the Tornu Maternity Hospital of Buenos Aires between the year 1934 up to the present.

From this large group, eleven infants who showed unmistakable evidence of congenital tuberculosis were reported and carefully studied.

He points out that the overwhelming majority of infants born to tuberculous mothers will grow and thrive nearly as well as those born from healthy mothers.

The rare infant who will show congenital tuberculosis is always the offspring of a severely and fatally infected tuberculous mother.

The author points out that in order to have fetal infection with tuberculosis there must be tuberculous infection of the placenta. The tubercle bacillus does not pass the sound placenta. He believes that hereditary resistance to tuberculous infection can be transmitted.

In a series of fine diagrams and microphotographs the author shows that the arrangement of the fetal circulation at the third month of intrauterine life favors the transmission of tuberculous infection derived from a tuberculous placenta.

The fetal organs such as the lungs, spleen, and liver which have the major blood supply at this age of the fetus will show the preponderant tuberculous infection and involvement.

The author believes that practically all of the cases of congenital tuberculous infection are of hematogenous origin derived from the blood passing through a tuberculous placenta.

The diagnosis of congenital tuberculosis in the infant can be made only if it is absolutely known that the infant was removed instantly after birth from the environment of the tuberculous mother.

The author believes that congenital tuberculosis in the infant is almost a preventable condition if diagnosis of tuberculosis in the pregnant mother can be established at the earliest possible moment and she then can be given the adequate care which modern medical and social service can provide.

The material in the monograph is presented admirably and the illustrations are excellent.

SCHLUTZ

The Journal of Pediatrics

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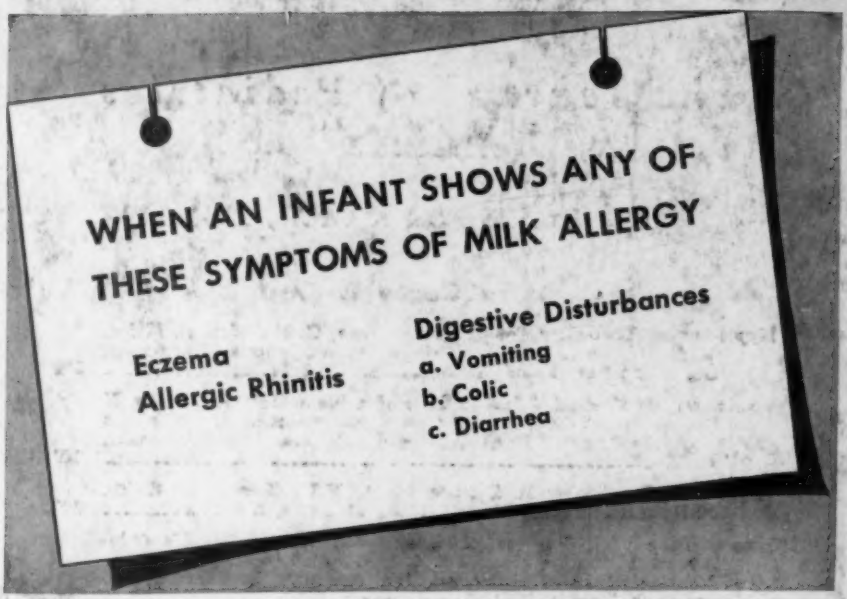

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